Growing from common ground: nontuberculous mycobacteria and bronchiectasis

Eva Van Braeckel [1,2,3] and Cédric Bosteels [1,2,3]

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Edited by James D. Chalmers, Felix C. Ringshausen and Pieter C. Goeminne

[1]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium. [2]Respiratory Infection and Defense Lab (RIDL), Department of Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium. [3]European Reference Network on rare respiratory diseases (ERN-LUNG).

Corresponding author: Eva Van Braeckel (Eva.vanbraeckel@ugent.be)

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The chicken or the egg? The complex interplay between bronchiectasis and nontuberculous mycobacterial pulmonary disease: clinical insights, common susceptibility factors and treatment strategies breaking new ground. https://bit.ly/3x0Zn2G

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Abstract

Bronchiectasis and nontuberculous mycobacteria (NTM) are intricately intertwined, with NTM capable of being both a cause and consequence of bronchiectatic disease. This narrative review focuses on the common ground of bronchiectasis and NTM pulmonary disease (NTM-PD) in terms of diagnostic approach, underlying risk factors and treatment strategies. NTM-PD diagnosis relies on a combination of clinical, radiological and microbiological criteria. Although their epidemiology is complicated by detection and reporting biases, the prevalence and pathogenicity of NTM species vary geographically, with *Mycobacterium avium* complex and *Mycobacterium abscessus* subspecies most frequently isolated in bronchiectasis-associated NTM-PD. Diagnosis of nodular bronchiectatic NTM-PD should prompt investigation of host factors, including disorders of mucociliary clearance, connective tissue diseases and immunodeficiencies, either genetic or acquired. Treatment of NTM-PD in bronchiectasis involves a multidisciplinary approach and considers the (sub)species involved, disease severity and comorbidities. Current guideline-based antimicrobial treatment of NTM-PD is considered long, cumbersome and unsatisfying in terms of outcomes. Novel treatment regimens and strategies are being explored, including rifampicin-free regimens and inclusion of clofazimine and inhaled antibiotics. Host-directed therapies, such as immunomodulators and cytokine-based therapies, might enhance antimycobacterial immune responses. Optimising supportive care, as well as pathogen- and host-directed strategies, is crucial, highlighting the need for personalised approaches tailored to individual patient needs. Further research is warranted to elucidate the complex interplay between host and mycobacterial factors, informing more effective management strategies.

Introduction

Bronchiectasis and nontuberculous mycobacteria (NTM) have been intertwined as a chicken-and-egg situation for decades. NTM species were linked to pulmonary exacerbations in bronchiectasis for the first time in 1992 [1], while in the same year, Reich and Johnson [2] first described nodular bronchiectatic NTM pulmonary disease (NTM-PD) due to *Mycobacterium* (*M.*) *avium* complex (MAC). The latter was aptly named Lady Windermere syndrome, after Oscar Wilde's play, because of the distinctive phenotype of the patients and the hypothesis that habitual voluntary suppression of cough may have led to engraftment of MAC in poorly draining lung regions such as the lingula and the middle lobe [2]. Although this hypothesis is now disputed, the term is still used to describe nodular bronchiectatic NTM-PD [3]. Nowadays, it is well established that NTM can be either the cause or a consequence of bronchiectatic disease, or even both, in view of the vicious vortex of bronchiectasis [4].

The prevalence of NTM in adults with bronchiectasis is on the rise according to a systematic review and meta-analysis examining literature between 2006 and 2021, with a prevalence of 10% and a predominance of MAC species (65–90%) [5]. However, many studies are hampered by a detection bias, as NTM will generally remain under the radar when clinicians do not specifically order a mycobacterial culture on a respiratory specimen. Moreover, there is a substantial reporting bias because most countries do not consider NTM species as reportable pathogens. In addition, the isolation of an NTM species does not necessarily indicate the existence of NTM disease. The prevalence and intrinsic pathogenicity of different NTM species tend to vary largely according to geographical factors [6–8]. This narrative review aims to highlight the complex interplay between underlying host factors, the propensity of a certain NTM isolate to cause disease within its epidemiological context and the clinical presentation of NTM infection in and/or as bronchiectasis. Starting from the current clinical practice guidelines [9, 10], we provide an overview of the treatment regimens and strategies that show potential in breaking new ground, with a focus on nodular bronchiectatic NTM-PD.

Search strategy

We conducted a literature search of Medline (PubMed) up to 19 March 2024. Both authors (E.V.B. and C.B.) independently carried out the searches. Search terms included combinations of "atypical mycobacteria", "non-tuberculous mycobacteria (NTM)", "NTM pulmonary disease (NTM-PD)", "nodular bronchiectatic disease", "bronchiectasis", "risk factors" and "*Mycobacterium avium*". The search results were screened for relevant titles and abstracts. Reference lists of included studies were reviewed to identify additional relevant studies.

NTM-PD

Diagnosis of NTM-PD requires a combination of clinical, radiological and microbiological criteria, including a positive mycobacterial culture from at least two separate sputum samples, at least one deep respiratory specimen (bronchial wash or bronchoalveolar lavage fluid) or compatible histopathology combined with culture positivity [11]. Table 1 summarises the diagnostic criteria proposed in 2007 by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) and recommended in the 2020 joint clinical practice guideline by the ATS, the European Respiratory Society (ERS), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the IDSA [10, 11]. Importantly, isolation of an NTM from a bronchiectasis patient does not counterpart the existence of NTM-PD, as contamination of respiratory samples by these ubiquitous organisms may occur, as well as transient infection and colonisation without overt associated disease (figure 1) [12]. Signs and symptoms of NTM-PD are considered nonspecific, range from mild to severe and are often difficult to distinguish from the underlying lung disease. Patients might present with respiratory symptoms, such as dyspnoea, (productive) cough or haemoptysis, and systemic symptoms, such as fatigue, anorexia, weight loss, fever and night sweats. From a radiological point of view, NTM-PD can classically present in two main forms, namely nodular bronchiectatic disease and fibrocavitary disease (figure 1) [13, 14]. In a recent study, a third radiological phenotype of MAC-PD was reported, characterised by radiological pleuroparenchymal fibroelastosis (PPFE) [15]. Whereas the prognosis of fibrocavitary disease and the PPFE phenotype is poor, the natural course of nodular bronchiectatic NTM-PD is often mild or benign.

TABLE 1 Diagnostic criteria for nontuberculous mycobacterial pulmonary disease (NTM-PD)

Clinical criteria	Pulmonary or systemic symptoms
and	
Radiologic criteria	Nodular or cavitary opacities on chest X-ray or an HRCT scan that shows bronchiectasis with multiple small nodules
and	**Appropriate exclusion of other diagnoses**
Microbiologic criteria	Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures *or* Positive culture results from at least one bronchial wash or lavage *or* Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture-positive for NTM

AFB: acid-fast bacilli; HRCT: high-resolution computed tomography. Adapted from the official American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) statement and official ATS/European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/IDSA clinical practice guidelines [10, 11].

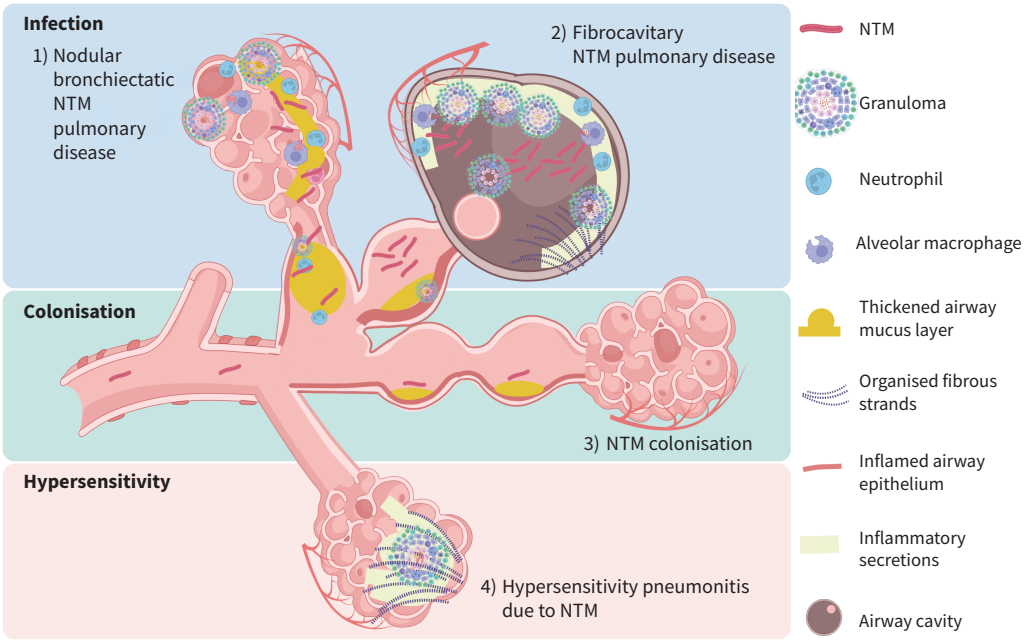

FIGURE 1 Nontuberculous mycobacteria (NTM) and the lung. NTM can cause a wide spectrum of disease in the human lung. While 1) nodular bronchiectatic and 2) fibrocavitary disease are manifestations of NTM pulmonary disease, NTM can also merely 3) colonise bronchiectatic airways, either transiently or chronically. A distinct, noninfectious, entity of NTM-related disease is 4) hypersensitivity pneumonitis due to NTM exposure. Created with BioRender with support from Iris Janssens.

In this review, we mainly focus on nodular bronchiectatic NTM-PD and discuss some of the risk factors associated with development and/or progression of the disease.

A distinct entity of NTM-related disease, outside the scope of this review, is so-called hot tub lung, a form of hypersensitivity pneumonitis (HP) in otherwise healthy patients exposed to NTM-contaminated water aerosols, mainly MAC species (figure 1). It is characterised by 1) respiratory symptoms such as dyspnoea and dry cough, 2) diffuse micronodular and/or ground glass opacities on high-resolution computed tomography, 3) bronchiolocentric granulomatous inflammation, and 4) culture of MAC species in the hot tub water or respiratory specimen. In contrast to NTM-PD, these patients do not present with productive cough and systemic symptoms such as fatigue, night sweats and weight loss, although fever might occur [16, 17]. Hot tub lung is currently not considered an infectious complication of exposure to NTM and an approach according to the current HP guidelines is recommended [18, 19].

NTM isolates in bronchiectasis

The term NTM refers to mycobacterial species distinct from those responsible for tuberculosis or leprosy. As opposed to *M. tuberculosis*, isolation of an NTM does not equal the existence of NTM disease and requires careful consideration of microbial and host factors. The most commonly identified NTM species related to pulmonary disease are the slow-growing MAC ones (including *M. avium* and *M. intracellulare* subsp.), *M. kansasii*, *M. malmoense* and *M. xenopi*, and the rapid-growing *M. abscessus*, *M. chelonae* and *M. fortuitum* [9, 10]. These species differ in their geographical distribution and in their propensity to cause pulmonary disease. *M. kansasii* for instance is considered to have high intrinsic pathogenicity, as opposed to *M. fortuitum* [6, 20–23]. While the virulence of NTM species seems to vary geographically as well, other species, such as *M. gordonae*, are rarely pathogenic and generally reflect contamination or transient colonisation [9]. In addition to the number of positive respiratory samples, the presence of sputum smear positivity (detection of acid-fast bacilli upon direct examination of sputum or a deep sample) is a predictor of disease progression and thus clinical significance [14, 24]. Certain NTM species may also predispose to particular radiological patterns. Overall, MAC and *M. abscessus* most often present with nodular bronchiectatic changes, while *M. kansasii*, *M. malmoense* and *M. xenopi* are more frequently associated with fibrocavitary NTM-PD [20, 21, 25]. Accurate identification of NTM species and subspecies using an inambiguous nomenclature (*e.g.* in the case of *M. abscessus* [26]) is therefore

essential as it can predict the clinical relevance of an isolate and aid in treatment decision-making, alongside clinical and radiological criteria.

Risk factors for NTM pulmonary disease

NTM are estimated to be found in nearly one in ten patients with bronchiectasis [25, 27, 28], which is considered the most significant risk factor for NTM-PD [29]. As mentioned earlier, whether bronchiectasis serves as a primary risk factor, reflects other underlying risk factors or whether it emerges as a consequence of NTM-PD is difficult to discern. Nevertheless, it seems that the risk factors for NTM infection are inherently linked to bronchiectasis. These factors encompass disorders of mucociliary clearance, alterations in airway mucus consistency, presence of connective tissue disorders, compromised immune responses and others [30]. Any of these factors, alone or in concert, could hamper clearance of NTM and other pathogens, leading to perpetual inflammation and bronchiectasis. As NTM are opportunistic pathogens in humans, diagnosing NTM-PD should prompt clinicians to investigate predisposing host factors (figure 2).

Disorders of mucociliary clearance

NTM-PD is more prevalent in patients with pre-existing chronic lung diseases such as COPD, asthma, interstitial lung disease, α-1 antitrypsin deficiency and bronchiectasis [29, 31, 32]. These conditions may

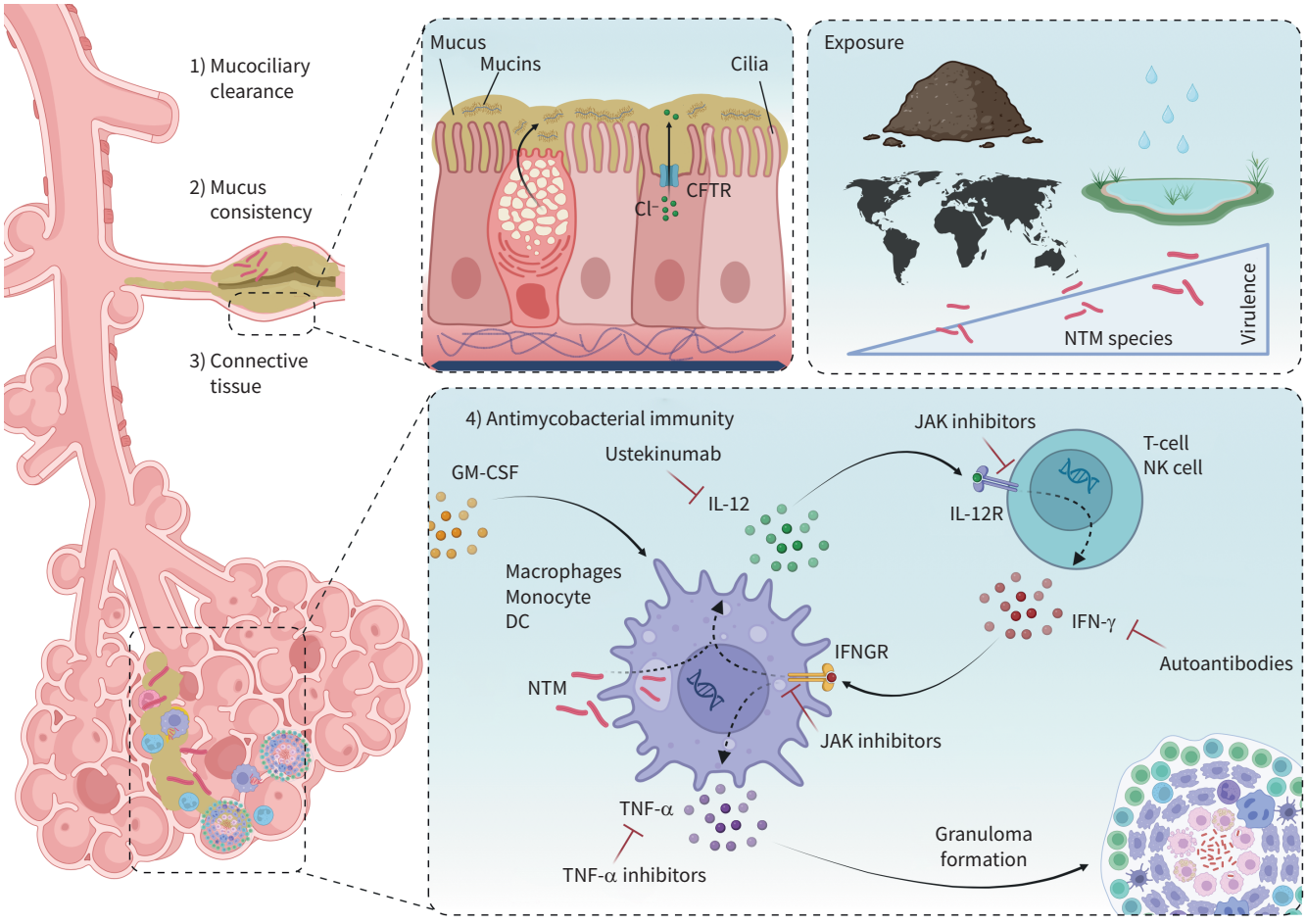

FIGURE 2 Host and environmental risk factors for nontuberculous mycobacterial infection. Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms mostly found in soil and water. The different NTM species differ in their geographical distribution and their potential to cause pathology. Bronchiectasis is the most significant risk factor for NTM-related pulmonary disease, and both conditions share risk factors that are related to 1) disturbed ciliary function, 2) abnormal mucus consistency, 3) connective tissue disease and/or 4) inappropriate immune responses. Antimycobacterial immunity depends on a reinforcing circuit of interleukin (IL)-12/interferon (IFN)-γ/tumour necrosis factor (TNF)-α signalling coordinated by mononuclear phagocytes and lymphoid cells. CFTR: cystic fibrosis transmembrane regulator; Cl^-: chloride; DC: dendritic cell; GM-CSF: granulocyte–macrophage colony-stimulating factor; JAK: Janus kinase; NK: natural killer; R: receptor. Created with BioRender.

predispose to NTM-PD by impaired mucociliary clearance, chronic inflammation and/or use of associated medication such as systemic or inhaled corticosteroids (ICS). Prior or concomitant tuberculosis may lead to structural lung damage, including bronchiectasis, and reflect poor antimycobacterial host responses, further increasing the risk of NTM-PD [29, 33–35]. Among adult patients with primary ciliary dyskinesia, an inherited ciliopathy, 18% was identified to have had at least one positive sputum culture for NTM [36]. Additionally, NTM-PD patients without an apparent pre-existing lung condition tend to have more variants in ciliary genes and a reduced ciliary beat frequency when compared to control subjects [30, 37].

Mucus consistency

Sputum of bronchiectasis patients contains higher mucin concentrations and is less hydrated [38]. This is also seen in cystic fibrosis (CF), an autosomal recessive disease caused by bi-allelic variants in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene. Dysfunction of the CFTR protein leads to water–electrolyte imbalance in the airways, thickened mucus secretions, reduced mucociliary transport, recurrent bacterial infections and structural lung damage (*i.e.* bronchiectasis) [39, 40]. Individuals with CF face a high risk of NTM-PD, with epidemiological studies reporting an NTM prevalence ranging from 6.6 to nearly 50% [41–47]. Remarkably, one out of every three to four non-CF patients diagnosed with NTM-PD was found to carry a single *CFTR* mutation [30, 31, 48], suggesting that subtle changes in homeostasis of airway surface liquid may also be critical in determining host susceptibility.

Connective tissue disease

In a whole-exome sequencing study of 69 patients with NTM-PD, heterozygous variants associated with connective tissue diseases such as Ehlers–Danlos syndrome were more frequently identified in patients with NTM-PD compared to controls [30]. A substantial proportion of patients with nodular-bronchiectatic NTM-PD have the Lady Windermere syndrome clinical phenotype [2, 49]. These individuals are usually nonsmoking, white, post-menopausal women with a slender habitus, scoliosis, pectus excavatum and mitral valve prolapse, who develop predominantly middle lobe and lingula bronchiectasis. A combination of variants in genes involved in connective tissue diseases as well as immune regulation, ciliary function, DNA damage response and mucus consistency (*e.g.* presence of a *CFTR* mutation in up to 50% of cases) were found more frequently in these patients compared to control subjects [30, 37, 50–53]. For instance, variants in the *macrophage stimulating 1 receptor* gene (*MST1R*) are associated with Lady Windermere syndrome and may lead to impaired airway ciliary function and reduced interferon gamma (IFN-γ) production in response to NTM [30, 49, 50].

Immunity against NTM

Mononuclear phagocytes such as alveolar macrophages and dendritic cells (DCs) are key in orchestrating the host immune response to NTM [47]. Following phagocytosis, these cells release the pro-inflammatory cytokine interleukin-12 (IL-12), which stimulates T-cells and natural killer (NK) cells to produce IFN-γ. Subsequently, IFN-γ licenses phagocytes to kill mycobacteria through induction of nitric oxide (NO) and reactive oxygen species. IFN-γ signalling also leads to further upregulation of IL-12 production and the release of tumour necrosis factor alpha (TNF-α) [54]. TNF-α, in turn, also plays a pivotal role in antimycobacterial defence by instigating macrophage activation and maintaining granulomata integrity [55–57]. The critical role of the IL-12/IFN-γ pathway in antimycobacterial immunity is underscored by the increased susceptibility to disseminated mycobacterial infection observed in patients with genetic [47] or acquired defects affecting any component of this axis.

Patients with inborn errors in the IL-12–IFN-γ axis (*e.g. IL12B*, *IFNGR1* and *STAT1*) or phagocyte function (*e.g. IRF8*, *GATA2* and *NRAMP1*) typically have early-life disseminated infection with weakly virulent NTM [47, 58]. Conversely, primary immunodeficiencies affecting humoral immunity, including X-linked agammaglobulinaemia and common variable immunodeficiency, are not directly associated with susceptibility to NTM-PD [59, 60]. However, patients with antibody deficiencies are more prone to bronchiectasis, which in turn can pose a higher risk for NTM colonisation or infection [32]. Even in patients without overt immunodeficiency, subtle impaired immune responses have been reported. For instance, *ex vivo* stimulated peripheral blood mononuclear cells isolated from patients with NTM-PD produce lower levels of IFN-γ and TNF-α [49, 61–63]. Other studies have reported an increased frequency of potentially significant polymorphisms in genes crucial for antimycobacterial immunity (*e.g. STAT1*, *IRF8* and *IFNGR1*) among NTM-PD patients compared with their relatives or healthy controls [30, 64].

Acquired immunodeficiencies leading to increased susceptibility of NTM infection include iatrogenic immunosuppression, malignancies, AIDS and anticytokine autoantibodies [29, 65–69]. Supporting the pivotal role of TNF-α in antimycobacterial immunity and granuloma integrity, the use of anti-TNF-α agents is linked to a higher risk of NTM disease [56, 69]. Other biologic agents targeting the IL-12–IFN-γ

axis, such as ustekinumab (anti-IL-12p40) and Janus kinase inhibitors, have a theoretical increased risk for NTM infection but limited safety data exist [32, 70]. Autoantibodies against IFN-γ have been described in elderly patients, often of Asian origin, with (disseminated) NTM infection and are associated with specific human leukocyte antigen alleles [65, 71–74]. While anti-IFN-γ autoantibodies are not routinely measured in the lab, it has been proposed to repurpose the mitogen control within an IFN-γ release assay as a screening tool in this setting, since the presence of anti-IFN-γ autoantibodies would result in undetectable levels of IFN-γ [75]. In addition, autoantibodies against granulocyte–macrophage colony-stimulating factor (GM-CSF) have been found in NTM-PD patients [76]. GM-CSF is essential for alveolar homeostasis and supports the activity of macrophages and other myeloid phagocytes like neutrophils and lung-resident DCs [77, 78].

Patients receiving medication that suppresses cellular immunity, such as chemotherapy in cancer or immunosuppressants (*e.g.* calcineurin inhibitors, corticosteroids and mycophenolate) for autoimmune disease or after solid organ or haematopoietic stem-cell transplantation, have an increased risk of NTM infection [67, 79–82]. Use of ICS has often been associated with an increased risk of NTM-PD [29, 33, 83]. Whether this is attributable to the underlying chronic respiratory disease or the immunosuppressive effects of ICS, or both, has been a matter of debate. However, recent studies support a causal link between ICS use and NTM-PD, as evidenced by the association between cumulative ICS use and an increased risk of developing NTM-PD, particularly with fluticasone use compared to budesonide [84, 85].

Macrolides are commonly prescribed for their anti-inflammatory properties in managing chronic respiratory diseases such as COPD, CF and bronchiectasis, often for prolonged periods. Despite its effectiveness in treating NTM-PD as the backbone of multi-drug regimens, the prolonged use of azithromycin in people with CF has been associated with a heightened risk of *M. abscessus* infection [41, 44]. This observation has been attributed to acquired or induced macrolide resistance, as well as azithromycin's dual effect on inhibiting phagolysosomal degradation of mycobacteria and suppressing the production of IL-12, IFN-γ and TNF-α [41, 44, 86]. However, according to a recent meta-analysis, the long-term use of macrolides was rather protective against overall NTM-PD, albeit not significantly [29].

Other risk factors

Several other risk factors have been suggested to contribute to NTM-PD. Gastro–oesophageal reflux disease (GERD) may occur silently and has been associated with both bronchiectasis and NTM-PD [87–89]. Isolation of certain rapidly growing NTM species from respiratory samples, such as *M. fortuitum* and *M. chelonae*, should raise the suspicion of underlying GERD [90]. Ageing seems to correlate with increased susceptibility [22, 29] and might reflect accumulated environmental events, structural lung damage and a decline in cellular immune responses, also known as immunosenescence [91]. Underweight and malnutrition are associated with an increased risk for NTM infection, while a protective effect is seen at higher body mass indices [29, 49, 92, 93]. Other risk factors include rheumatoid arthritis, vitamin D deficiency, high socioeconomic status and long-term antibiotic usage [94–98].

Treatment of NTM infection in bronchiectasis

NTM infection is considered one of the multiple treatable traits in bronchiectasis [4]. However, it is important to emphasise that the diagnosis of nodular bronchiectatic NTM-PD does not automatically mandate antimicrobial treatment. Identifying who, how and when to treat requires integration of not only the diagnostic criteria, but also of other elements such as host factors, disease severity and progression over time, and clinical relevance of the isolated NTM species in itself and within a certain clinical context such as immunosuppression [14]. In many cases this will involve multidisciplinary team and/or expert consultation and consideration of different treatment modalities, including watchful waiting (figure 3). To treat or not to treat is a question that is challenged by the fact that multidrug antibiotic regimens for NTM-PD are lengthy and cumbersome, frequently involve adverse events, and often associated with a poor outcome. In MAC-PD for instance, only 61–66% of patients achieve sustained culture conversion with the recommended triple-drug regimens [99]. On the other hand, guideline adherence in NTM-PD management has proven inadequate throughout the world, holding risks of inducing further antimicrobial resistance [100–102]. Optimising treatment strategies on different levels, namely supportive, antimicrobial and host-immunity directed, is therefore one of the key priorities in the NTM field.

Supportive treatment

Airway clearance is the mainstay of bronchiectasis management and is crucial in caring for a patient with NTM-PD. Moreover, patients with pulmonary NTM infection will require life-long attention to their bronchiectasis, irrespective of the status of their NTM infection, namely cured, cleared or persistent [103]. Limited data are available on airway clearance techniques and pulmonary rehabilitation specifically for

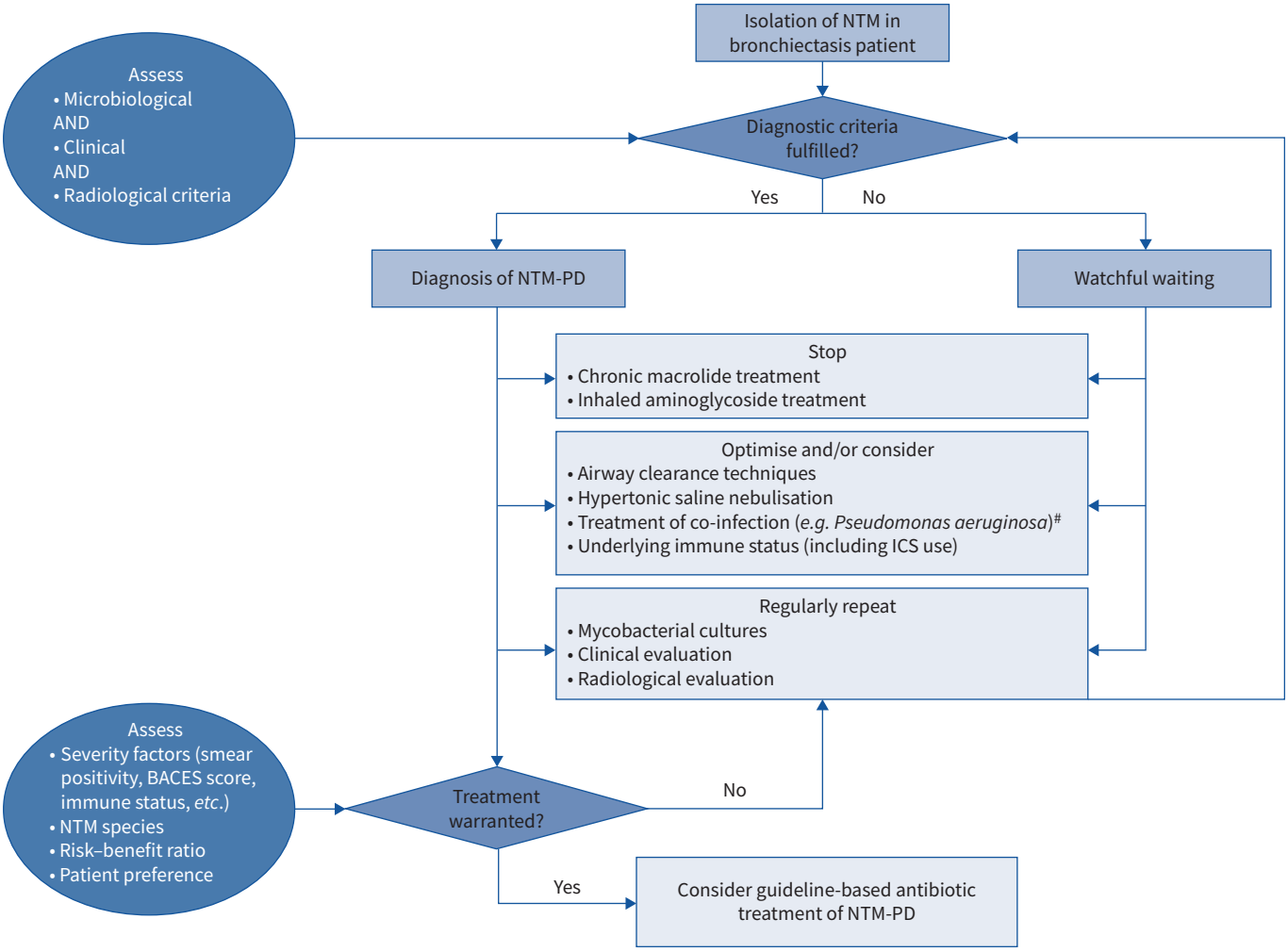

FIGURE 3 Decision tree for management of nontuberculous mycobacteria (NTM) in bronchiectasis. #: avoid using antibiotics with activity against NTM, such as aminoglycosides, for treatment of co-infections. BACES: body mass index, age, cavity, erythrocyte sedimentation rate and sex [117]; ICS: inhaled corticosteroids; NTM-PD: NTM pulmonary disease.

NTM-PD [104, 105]. However, the application of current physiotherapy recommendations for bronchiectasis, including active cycle of breathing techniques, autogenic drainage and positive expiratory pressure devices, seems reasonable in NTM-PD patients to reduce the impact of cough, improve quality of life and reduce exacerbation risk [106].

In addition to physiotherapy, hypertonic saline (HS) nebulisation is currently used in many NTM reference centres due to its ability to enhance clearance of airway secretions in bronchiectasis [107]. Whether HS might also exert direct antimycobacterial effects still remains to be established. A small proof-of-concept study has observed both killing of *M. avium* and growth inhibition of *M. abscessus* when exposed to HS (5.8%) *in vitro* and very tentatively suggested a beneficial effect of HS inhalation in a retrospective cohort, including on sputum culture conversion [108]. Two open-label randomised controlled trials (RCTs) in MAC-PD are currently ongoing, one comparing HS (7% or 3% in case of poor tolerability of the 7% NaCl solution) with guideline-based therapy (GBT), using culture conversion at 12 weeks as the primary outcome [109] and a second investigating changes in health-related quality of life after 4, 8 and 12 weeks of HS (5.8%) inhalation plus best supportive care *versus* best supportive care alone [110].

While specific treatment of NTM infections falls beyond the scope of the current ERS and British Thoracic Society bronchiectasis guidelines, excluding active NTM infection prior to long-term antibiotic treatment or immunomodulatory macrolide maintenance therapy is considered good practice in bronchiectasis patients [111, 112]. As macrolide monotherapy is associated with induction of macrolide resistance in

NTM [113–115], isolation of an NTM in a respiratory specimen of a patient on chronic macrolide treatment to prevent frequent exacerbations in bronchiectasis might prompt cessation of the drug. Another precautionary approach might be to avoid systemic or inhaled aminoglycoside antibiotics (*e.g.* amikacin or tobramycin) outside the setting of guideline-based mycobacterial treatment regimens in bronchiectasis patients with a positive NTM culture. However, to the best of our knowledge, no supportive evidence has yet been reported. This might be the case in bronchiectasis patients treated for acute or chronic infection with *Pseudomonas aeruginosa* for instance. If possible, an NTM-sparing regimen might be preferred in the case of co-infection with NTM species. Sputum cultures may yield (false) negative results in patients using macrolides or other antibiotics that could impair NTM growth (*e.g.* aminoglycosides, co-trimoxazole, fluoroquinolones or linezolid). If clinical suspicion of NTM-PD is high, it is advisable to repeatedly collect samples after discontinuing these antibiotics. If sputum cultures continue to yield negative results, performing sputum induction or a computed tomography directed bronchial lavage to obtain good quality respiratory samples should be considered.

Patients with NTM-PD are ideally managed in experienced centres with a multidisciplinary team comprising pulmonologists, infectious disease specialists, microbiologists and radiologists, alongside paramedics such as pharmacologists, dieticians, psychologists and physiotherapists. This multidisciplinary team can holistically address diagnostic and therapeutic challenges faced by NTM-PD patients. Attention to the management of comorbidities, predisposing factors and treatable traits, irrespective of their association with bronchiectasis and/or NTM-PD, can improve overall outcomes beyond the antimycobacterial treatment. When antimycobacterial treatment is indicated, it is important that it is prescribed in accordance with current guidelines, taking into account potential adverse effects and interactions with co-administered medications. In NTM expertise centres, it is standard practice to optimise the physical and nutritional status of NTM-PD patients.

Hence, the multidisciplinary evaluation for initiating antimicrobial treatment in nodular bronchiectatic NTM-PD alongside supportive measures requires careful assessment to balance potential risks and benefits tailored to each individual patient's situation [9, 10]. Ultimately, the physician and patient should collaboratively define individual treatment goals and strategies [116].

Antimicrobial treatment

As described above, the decision whether or not to treat NTM-PD with antimicrobial therapy depends on the identified species, bacterial load (*i.e.* smear positivity), drug susceptibility testing (DST), disease severity and patient-specific factors such as comorbidities. Assessing the risk factors associated with progression or mortality can assist clinicians in their decision to start antimicrobial treatment. For instance, the body mass index, age, cavity, erythrocyte sedimentation rate and sex (BACES) score based on five variables (body mass index $<18.5\ kg \cdot m^{-2}$, age $\geqslant 65$ years, presence of cavity, erythrocyte sedimentation rate and male sex) has been shown to predict mortality among patients with NTM-PD [117]. Treatment guidelines and consensus recommendations on management of pulmonary disease caused by specific NTM species have been proposed and are referred to as GBT [9, 10, 118]. For MAC, the most common NTM found in bronchiectasis patients, this typically implies combination therapy with a macrolide, ethambutol and a rifamycin, given until 12 months after culture conversion. Integration of DST into the treatment regimen choice is recommended for macrolides and amikacin in MAC and *M. abscessus*, and for rifampicin in *M. kansasii* pulmonary disease [10]. In nodular bronchiectatic macrolide-susceptible MAC, intermittent (three times weekly) treatment regimens are still supported by the ATS/ERS/ESCMID/IDSA guidelines, a practice that is considered standard in most North American centres based on noncomparative case series ([10] and references therein). However, a recent retrospective cohort study indicated that intermittent treatment led to a lower culture conversion rate than daily treatment in sputum smear positive patients with nodular bronchiectatic MAC-PD [119]. The results of the first RCT comparing intermittent *versus* daily treatment of noncavitary MAC-PD were recently made publicly available [120]. This Japanese multicentric trial addressed both efficacy and tolerability and uses the proportion of patients requiring initial regimen modification as the primary end-point [121]. The study, however, failed to demonstrate that intermittent treatment with clarithromycin, rifampicin and ethambutol was better tolerated than daily treatment and found no significant difference in efficacy [120]. In cavitary, advanced/severe or macrolide-resistant disease, addition of an intravenous aminoglycoside (amikacin or streptomycin, three times weekly, may be used) to the initial daily oral treatment regimen is to be considered for at least 2–3 months [10]. Based on the results of the CONVERT trial, amikacin liposomal inhalation suspension (ALIS) has been proposed for refractory MAC-PD, defined as MAC-positive sputum cultures despite at least 6 months of stable GBT, and for MAC-PD patients with limited treatment options [10, 122, 123]. Notably, in the CONVERT trial, only 29.0% of patients treated with ALIS in addition to GBT

achieved culture conversion after 6 months, while nearly 90% of patients experienced adverse effects such as cough, dyspnoea and dysphonia.

Current guidelines still prefer a three-drug macrolide-containing regimen over a two-drug macrolide-containing one for initial therapy of MAC-PD. The primary roles of ethambutol and the rifamycin in this regimen are to prevent the induction of macrolide resistance [10]. The role of rifampicin in MAC-PD has become a matter of debate for multiple reasons, namely a lack of *in vitro* bactericidal effect against MAC, the occurrence of adverse events and pharmacokinetic interactions – particularly those resulting in reduced bioavailability of the crucial macrolide backbone through CYP3A4 induction [124–127]. Different strategies to replace or avoid rifampicin in MAC treatment are currently under investigation. Preliminary and retrospective studies have suggested the noninferiority of dual treatment with ethambutol and azithromycin or clarithromycin, compared to a three-drug regimen with rifampicin, including reassuring data on the incidence of macrolide resistance acquisition [128–130]. The validity of a rifamycin-free regimen remains to be confirmed in RCTs, such as the MAC2v3 trial, which randomises between a three times weekly regimen of azithromycin and ethambutol with or without rifampicin in adults with nodular bronchiectatic MAC-PD [131]. The efficacy of a two-drug rifampicin-free regimen of azithromycin and ethambutol in milder manifestations of MAC-PD is supported by recent *in vitro* data in a hollow-fibre model simulating epithelial lining fluid pharmacokinetics, showing that rifampicin adds no bactericidal capacity to the two-drug backbone and does not impact the emergence of macrolide resistance in this experimental setting [127].

Another strategy of interest with an increasingly available body of evidence is replacing rifampicin with clofazimine, an antimicrobial riminophenazine dye primarily used to treat *M. leprae*. In the same hollow-fibre *M. avium* infection model, exchanging rifampicin for clofazimine improved the antimycobacterial activity of combination therapy with azithromycin and ethambutol [132]. Clofazimine-based regimens have shown promise in earlier observational and retrospective studies [133, 134]. Interestingly, besides its direct antimicrobial activity, clofazimine is known to exert *in vitro* synergistic effects with amikacin on both rapidly and slowly growing NTM, including *M. abscessus*, MAC and *M. simiae*, possibly through its cell wall-destabilising properties allowing increased influx of other drugs with intracellular targets [135]. A small retrospective cohort study in Nijmegen, Netherlands, showed favourable outcomes in patients with severe MAC-PD (either fibrocavitary or nodular bronchiectatic) who were treated with quintuple therapy including add-on systemic amikacin and clofazimine *versus* standard triple therapy [136]. This was followed by the PERC randomised trial, recently published by the same group, which evaluated clofazimine *versus* rifampicin as adjuncts to an ethambutol–macrolide regimen in a noninferiority design in MAC-PD. While noninferiority could not be statistically proven due to recruitment issues, both arms performed equal on the primary outcome of sputum conversion at 6 months (58% in the rifampicin group *versus* 62% in the clofazimine group) [137]. The frequency of adverse events was similar with both regimens, while their nature differed, with diarrhoea occurring more frequently in the clofazimine arm and arthralgia in the rifampicin arm. Of note, the same azithromycin dose (500 mg daily) was used in both arms, unsurprisingly leading to higher maximum concentrations of azithromycin in the rifampicin-free regimen [137]. The authors conclude that a clofazimine–ethambutol–macrolide regimen should be considered in the treatment of MAC-PD. Additionally, there is a need for further investigation into the correlation between plasma concentrations and both the tolerability and efficacy of antimycobacterial drugs. Studies have shown that higher plasma levels of azithromycin or clofazimine are associated with more favourable microbiological responses [126, 137].

The place of ALIS in initial treatment of MAC-PD also remains to be established. The phase 3 ARISE and ENCORE studies in newly diagnosed nodular bronchiectatic MAC-PD use a background regimen of azithromycin and ethambutol plus placebo (*i.e.* empty liposome control) as the comparator arm for a novel three-drug regimen with azithromycin, ethambutol and ALIS [138, 139]. While the ENCORE study is ongoing, preliminary results from ARISE were recently presented at the ATS conference, indicating statistically significant higher culture conversion rates at month 7, *i.e.* 1 month after cessation of a 6-month treatment course, with the ALIS-based regimen (78.8%) compared to dual therapy with azithromycin and ethambutol (47.1%); findings that however still need to undergo peer review [140]. Although currently only licensed for MAC infections, ALIS has recently also shown promise in *M. abscessus* lung disease in mixed CF/non-CF populations in retrospective cohort studies and in one noncomparative open-label trial [141–143].

Many other antimicrobial strategies remain to be further evaluated for NTM-PD (reviewed in [144–146]), including new formulations of existing drugs such as inhaled clofazimine [147], repurposed drugs licensed to treat multidrug-resistant tuberculosis such as bedaquiline [148], novel molecules within existing antibiotic classes such as omadacycline [149] and the newer oxazolidinone tedizolid [150], and bacteriophage therapy, which has been explored primarily in *M. abscessus* infections up to date [151].

Host-directed therapy

Personalised therapies aiming at restoring the immunological disbalance and supporting the host response to NTM can prove effective independently of antimicrobial drug susceptibility (comprehensive overview in [152]). Therefore, clinicians should attempt to identify aetiologic or associated host factors in patients with bronchiectasis and NTM-PD, as managing these factors specifically can improve overall outcome.

An obvious first step to consider is the reduction or cessation of immunosuppressive medication. This includes tapering or stopping ICS use if not strictly indicated and/or switching from fluticasone to a lower potency ICS.

In individuals with specific traits such as partial CFTR dysfunction in heterozygous *CFTR* mutation carriers, future studies should investigate whether restoring CFTR function improves NTM clearance, similar to what has been observed after introduction of CFTR modulator therapy in people with CF [153, 154]. In bronchiectasis patients, tackling neutrophilic inflammation through dipeptidyl peptidase-1 or cathepsin C inhibitors, such as brensocatib and BI 1291583, is a promising strategy to reduce pulmonary exacerbation frequency [155]. Their potential influence on NTM acquisition and infection course, however, remains to be examined, as patients with recent NTM infection were excluded from the past and ongoing trials [156, 157].

Enhancing antimycobacterial immune responses can be achieved by promoting phagosomal mycobacterial degradation, vaccination and/or cytokine therapies. Adjuvant therapy with IFN-γ or GM-CSF in NTM-PD is an attractive approach given their role in antimycobacterial immunity. In a case report of a patient with functional IFN-γ deficiency and NTM-PD, inhaled IFN-γ resulted in NTM culture conversion [158]. However, in an RCT of 91 patients with cavitary and noncavitary pulmonary MAC infection, the addition of inhaled IFN-γ to three times weekly GBT did not result in improved outcomes compared to GBT alone [159]. In another RCT, intramuscular IFN-γ for 6 months in addition to GBT in a similar patient group, resulted in a higher treatment response relative to placebo [160]. Adjuvant GM-CSF has shown to enhance antimycobacterial immunity in AIDS patients infected with NTM [161, 162]. In two CF patients with refractory pulmonary *M. abscessus* infection, adjuvant GM-CSF was associated with clinical, radiological and microbiological improvement [163]. In the OPTIMA trial, a small open-label pilot trial, the addition of inhaled GM-CSF to GBT led to sputum culture conversion in eight out of 32 patients with refractory NTM-PD [164]. Another immunomodulating therapy of interest in NTM-PD is inhaled NO. Although well-tolerated, outcomes seem variable and more trials investigating the efficacy of inhaled NO in patients with NTM-PD are warranted [165–168]. In patients with NTM infection and anticytokine autoantibodies, such as anti-IFN-γ, different approaches have been described in case reports to deplete these autoantibodies including intravenous immunoglobulins, plasmapheresis, cyclophosphamide and/or rituximab [66]. Use of checkpoint inhibitors, such as the PD-1/PD-L1 inhibitors commonly employed in cancer therapy, theoretically offers an attractive strategy to enhance T-cell effector functions in NTM infections [169]. However, concerns have been raised about na enhanced susceptibility to NTM-PD associated with checkpoint inhibitors, possibly due to dysregulated antimycobacterial immune responses [170, 171].

Conclusions

There are multiple facets to the liaison between bronchiectasis and NTM, including a complex interplay between underlying host factors and the intrinsic virulence of specific NTM species. The prevalence of NTM in bronchiectasis is on the rise and accurate diagnosis and management of NTM-PD are essential in improving patient outcomes. Isolating an NTM species in a bronchiectasis patient therefore always warrants careful consideration and appropriate action (figure 3). Identification of NTM species is crucial as it can predict the clinical relevance of an isolate. At the host level, NTM infection and bronchiectasis have many risk factors in common and appropriate aetiological investigations should be considered taking the disease severity into account. NTM-PD susceptibility may be defined by an unfortunate combination of gene variants that impact mucociliary clearance, mucus consistency, connective tissue and antimycobacterial immunity, along with environmental and iatrogenic factors.

Treatment of NTM infection in bronchiectasis requires a comprehensive and multidisciplinary approach that considers the diagnostic criteria, host factors, disease severity and clinical relevance of the isolated NTM species. These elements will guide the decision whether or not to install antimicrobial therapy concordant with current guidelines and consensus recommendations. Challenges such as lengthy treatment regimens, adverse events and antimicrobial resistance underscore the need for optimisation of treatment strategies, including rifamycin-free regimens. Supportive treatment, including airway clearance techniques with or without HS nebulisation, is essential in improving outcomes of both bronchiectasis and NTM-PD. Host-directed therapies aimed at restoring immunological balance and enhancing antimycobacterial

immune responses offer promising avenues for improving outcomes in NTM-PD. However, further clinical research is needed to explore the efficacy and safety of these approaches and therapeutic targets.

In summary, management of NTM infection in bronchiectasis requires a multidisciplinary approach, integration of diagnostic criteria and host factors, and optimisation of treatment strategies. A better understanding of the host and mycobacterial factors contributing to the susceptibility of NTM infection might lead to therapies specifically targeting these risk factors. All these approaches will require optimal patient selection and further clinical investigation in RCTs. Continued research efforts, ideally involving intense multinational collaboration between NTM expert centres, are essential to address the challenges posed by these micro-organisms, which are ubiquitous yet rarely disease-causing.

Points for clinical practice

- Screening for NTM in bronchiectasis patients is recommended, particularly before initiating long-term macrolide treatment.
- Clinical significance of NTM isolates in bronchiectasis patients depends on the NTM species, mycobacterial load, presence of clinical and radiological features, underlying disease severity, and host immune status.
- When an NTM is isolated from bronchiectatic airways, ordering DST (for macrolides and aminoglycosides) is recommended and cessation of any macrolide or (inhaled) aminoglycoside monotherapy is considered good practice until further work-up.
- Identify patients with increased susceptibility and contributing host factors and take action accordingly (*e.g.* tapering or stopping immunosuppression such as ICS).
- Carefully consider whether to treat or not to treat with guideline-based antimicrobial therapy and always optimise underlying and comorbid conditions. Watchful waiting also implies optimisation of bronchiectasis and comorbidity management and systematic follow-up.
- Consider expert advice in case of doubt.

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