



Editorial

Atypical Mycobacteria in Bronchiectasis. When do we Treat it?☆

Micobacterias atípicas en las bronquiectasias: ¿cuándo tratar?

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The clinical management of infections caused by non-tuberculous mycobacteria (NTM) is one of the main challenges of modern respiratory medicine, and a frequent topic of multidisciplinary discussion. NTM include all mycobacteria that are not *Mycobacterium tuberculosis* or *Mycobacterium leprae*, thus encompassing a wide and heterogeneous group of species that share characteristics such as their ubiquitous presence, with reservoirs in water, soil, animals, and humans, and their lack of virulence in the absence of predisposing factors. Infection is caused by environmental exposure to the reservoir, while transmission between humans has been described in patients with cystic fibrosis (CF).¹ The clinical picture and prognosis of the infection will vary depending on the species causing the infection (the most common are *M. avium complex*, *M. abscessus*, and *M. fortuitum*) and the patient's comorbidities; the main manifestation in all cases is pulmonary involvement.

The worldwide incidence and prevalence of pulmonary disease caused by NTM has been steadily increasing, to the extent that it is now more common than *M. tuberculosis* in developed countries,² although these figures are not totally dependable as notification is not mandatory. Greater awareness among medical professionals and improvements in laboratory techniques can explain in part this increase in NTM detection; however, factors such as population aging, associated comorbidities, and the rising population of immunosuppressed patients (due to a greater number of transplanted patients, development of biologics, etc.) are contributing to an increase in opportunistic infections, including NTM. NTM, for example, is one of the clinical criteria for acquired immunodeficiency syndrome in patients infected with human immunodeficiency virus. Moreover, the abuse of antibiotics over the world increases antibiotic pressure in the airway and could be selecting for microorganisms, such as NTM, that are less sensitive to single-agent antibiotics, and/or resistant strains with a poorer response to conventional antibiotic regimens.³

Although the pathophysiology of infection by NTM has not been fully characterized, associations with immune alterations

(primary or secondary)⁴ and other risk factors, such as low body weight, rib cage abnormalities, or respiratory diseases including silicosis and chronic obstructive pulmonary disease (COPD)⁵ have been described. Of these, concomitant bronchiectasis is associated with much higher relative risk of NTM infection than any other condition.⁶

The prevalence of bronchiectasis has dramatically increased in recent years, and is now the third most common respiratory disease after asthma and COPD.^{7–9} One of the main complications in patients with bronchiectasis is chronic bronchial infection, the specific management of which is one of the priorities of current research in this field. The prevalence of NTM in patients with bronchiectasis is estimated to be 9%–12%,^{10,11} and the presence of this pathology is considered both a cause and consequence of the disease. For this reason, the recent Spanish and European bronchiectasis guidelines^{12,13} propose that mycobacteria in sputum be investigated during the diagnosis of the disease and routinely in the follow-up of these patients, especially in candidates for chronic treatment with macrolides, due to the risk of selection of resistant strains and poorer response to treatment.¹⁴

Despite the increase in prevalence and scientific advances, the clinical management of pulmonary disease caused by NTM remains complex, to the extent that the recent British guidelines on NTM published in 2017¹⁵ maintain the same diagnostic criteria as proposed by the ATS in 2007.¹⁶

A survey recently conducted in several countries throughout the world detected a very poor adherence to clinical guidelines (17% overall; 9% in Europe) on the part of the professionals,¹⁷ probably due to the lack of awareness of these protocols. This, along with the lack of specific symptoms or diagnostic biomarkers and slow growth in microbiological cultures, often causes a delay in diagnosis, complicating even further the management of these infections. NTM, moreover, is usually isolated in a context of multimorbidity (including patients with chronic respiratory symptoms similar to COPD or bronchiectasis), making it difficult to apply diagnostic criteria in daily clinical practice.

The decision to start treatment must be the result of a case-by-case risk-benefit analysis. The main goal of treatment will always be symptomatic recovery, which along with radiological improvement and negativization of cultures, will guide the duration and effectiveness of the intervention. When assessing the need for treatment, the comorbidities of the patient and potential

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adverse effects of treatment and drug–drug interactions should be taken into account, as well as the virulence of the species of NTM, the potential response to treatment and, finally, the informed decision of the individual.

Once the decision to start treatment has been made, it is important to determine the antibiotic regimen recommended for each species of NTM on the basis of the results described in the literature, taking into account the lack of correlation between *in vitro* susceptibility testing and *in vivo* response. In many cases, it will also be essential to optimize the treatment of comorbidities and other non-pharmacological aspects, such as physiotherapy or nutrition.

In summary, NTM are a heterogeneous group of bacteria that mainly affect patients with a risk factor, one of which is the presence of bronchiectasis. In recent years, both the diagnosis of bronchiectasis and the prevalence of NTM infection have increased significantly; however, there is no global consensus regarding the criteria for treating the infection. The decision, therefore, will depend on the risk–benefit ratio in each case. In our opinion, not all factors carry the same weight. Given the frequent fragility of these patients, their general condition will be the main factor to consider in decision-making, followed by the potential adverse effects of treatment. The virulence of the species causing the infection and poor clinical response in many cases will be other factors for evaluation. Similarly, the optimization of other factors, such as physical therapy and nutrition, is key in the overall treatment of the patient, beyond the antibiotic regimen itself.

There is still a long way to go in the management of NTM infection. The main weaknesses in our approach must be addressed in the immediate future, and we must work to optimize microbiological techniques, to discover reliable biomarkers both for diagnosis and follow-up and, especially, to enhance awareness of the current clinical guidelines.

Conflict of interests

EP has received consulting and speaker's fees from Bayer, Menarini, Grifols, Zambon, Pfizer, Insmad, Polyphor, and Chiesi.

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