Review Article

Nontuberculous mycobacteria and bronchiectasis

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ABSTRACT

Non-tuberculous mycobacteria (NTM) are ubiquitous microorganisms in our environment. Although data are not truthful, we can say that we are experiencing an increase in the incidence-prevalence of infections by these microorganisms, especially in vulnerable population such as those with certain respiratory diseases, such as bronchiectasis (BQ). In all species NTM, the most studied is Mycobacterium avium complex, although the M abscessus is considered the most serious species in cystic fibrosis (CF) and M. xenopi in non-CF BQ. They described five clinical forms, the most frequent nodular/bronchiectasis and severe disseminated. The diagnosis of NTM lung disease in BQ is complicated, and continues to rely on three variables: clinical, radiological and microbiological. Given this difficulty, many suggest an observation period before starting a treatment, not always well tolerated and with side effects. Although morbidity and mortality is not high, they have been described risk factors that make it essential early treatment to avoid further serious complications.

Key words: Bronchiectasis, diagnosis, nontuberculous mycobacteria, treatment, prognosis

INTRODUCTION

Nontuberculous mycobacteria (NTM) are ubiquitous agents. There are described more than 160 species, some of which may lead sometimes to pulmonary disease.[1,2] The person–person or animal–person transmission is very rare, so it is considered that the external environment is the source of infection.[2,3]

NTM can be divided into two groups depending on the speed of its growth: (1) Those fast growing, needing less than 7 days to complete their growth in culture (*Mycobacterium abscessus*) and (2) slow growth, requiring more than 7 days to complete (*Mycobacterium avium complex* [MAC] and *Mycobacterium kansasii*).[2]

PREVALENCE

According to different jobs review, patients with bronchiectasis (BQ) have a frequency of developing disease NTM ranging from 5% to 30%.[4,5] In general, it has shown an increased prevalence in recent years, being in the USA of 6.6/100,000 h and Wales and Northern Ireland of 2.9/100,000 h.[6,7]

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Many studies have also shown an increase in the incidence of NTM in patients with BQ.[6] According to a recent meta-analysis, the work carried out in this field so far are scarce and few patients. The conclusions reached were that published data are more credible if: The sample size is ≥100, the post-2002 publications are still retrospectives, and geographical location was Asia.[8] This is because the more recent studies are the better study skills in micronucleus test (MNT) and are thought more frequently in patients with BQ, without forgetting that the means of transmission, especially contaminated water, are more common in our days and in areas such as Asia.

When the prevalence of certain species of MNT in BQ was analyzed, it was found that the MAC lung disease was of 13–81%, *Mycobacterium chelonae*, *Mycobacterium fortuitum*, and *M. abscessus* of 43–81%. Interestingly, when compared with the general population, the latter was affected especially by *M. kansasii and Mycobacterium xenopi*, with prevalence 10%.[8]

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PATHOGENESIS

The three most important factors in the pathogenesis of NTM infection are:

- Exposure: Because they are ubiquitous, how to acquire probably be inhaled directly from the water or hot water systems[2]
- Pulmonary pathology base: All those who have impaired mucociliary or epithelial damage system are predisposed to NTM infection
- Defects of immunity: Since not all patients in contact with a contaminated environment develop NTM disease, a failure of immunity is postulated. Innate immunity is involved in the activation of antimicrobial activity, phagocytosis of NTM, and modulating adaptive immune response activity.[10] We found relations with the human leukocyte antigen system so that in those with certain defects of it would have a predisposition, both NTM lung disease as the worsening of it.[11,12] In mice, it has been found that the long-term azithromycin could favor *M. abscessus* infection by damaging cell phagocytic capacity and also found cystic fibrosis (CF) transmembrane conductance regulator gene mutations in patients without CF BQ, which would mean an association with the transmembrane ion and water transport.[13] Other factors that compromise systemic immunity, such as diabetes mellitus, transplantation, or neoplasms, favor NTM infection.[2]

CLINICAL AND RADIOLOGICAL FEATURES

There have been described five clinical forms, especially with the MAC: (1) Nodular/bronchiectasis disease (NB); (2) cavity lung disease (CLD); (3) solitary pulmonary nodule; (4) extensive disease (ED); and (5) hypersensitivity-like disease.[7]

One question that many authors make is: What is the first? BQ or pulmonary NTM infection? Which is not yet resolved. It is clear that diseases such as CF or posttuberculous infection precede BQ.[8] Although it has always been said that the cause of NTM is BQ, there is so far little evidence. Infection seems NTM cause destruction of bronchial cartilage and muscle layer, granuloma formation, and ulceration of the bronchial mucosa so that could subsequently lead to the development of BQ.[14]

Of these, NB is the most typical form and has been associated with nonsmoking women, postmenopausal, affecting the middle lobe or lingula.[4,15,16] Although data on the disease FC do not match, they have been associated with men aged 40–50 years and even with over 70 years.[8,17]

In general, most authors have shown that long-term survival after suffering a form NB is good although described radiological deteriorations in following 10 years.[7,18] It has also been shown that following the natural history of disease, 40% never worsened after 2 years of follow-up.[19]

Comparing radiological forms with different species of NTM, it was found that MAC was associated with BQ (42%) and consolidations (43%), *M. chelonae*/*M. abscessus* cavitation (37%), *M. kansasii* to BQ (9%), cavitation (15%), and consolidations (13%).[2] When compared the cavity forms produced by a MNT against tuberculosis, the first affecting more middle lobe and lingula, are thin-walled and >3 cm.[20]

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DIAGNOSIS

Diagnosis is complicated because there may be the possibility of contamination or simply colonization without clinical manifestation. According to the criteria of the American Thoracic Society (ATS),[4] there must be two clinical criteria: symptoms and radiological findings and one

microbiological (in this case, and with the high possibility of contamination, is required more than one positive sample). In the case that exists clinical criteria, but without result in sputum, a single sample is required from bronchoscopy. It is not known today, the value of aspiration of lymph nodes (endobronchial ultrasound transbronchial needle aspiration), although they have reached the 69% diagnosis of mediastinal granulomatous disease.[21]

Although with limitations, molecular tests are being effective for the rapid identification of NTM species most frequently.[22]

A major problem is coinfection by other microorganisms, such as *Pseudomonas aeruginosa* (25–50%), *Staphylococcus aureus* (28%), *Haemophilus influenzae* (12%), and *Stenotrophomonas maltophilia* (4%); fungi can also coexist as *Candida albicans* (8%) or *Aspergillus Fumigatus*,[4] and even *Nocardia* species, other species of NTM or other genotypes of the same species of NTM (very typical with the MAC) that often cause relapses.[2]

RISK FACTORS OF MORTALITY

According to a systematic review on this topic and the heterogeneity of the studies, the data found are very different.[23] Of all NTM, MAC is the one that produces most frequently NTM lung disease.[7] It has been shown that the clinical forms more associated with mortality are ED and CLD in immunosuppressed patients such as HIV.[15] Mortality will depend on certain factors although most are medical literature data on the radiological nodular form/BQ and MAC.[16]

Factors, such as comorbidities, weight loss, low body mass index (BMI), anemia, or elevated systemic inflammation factors, are more found in the disease CLD and CLD + NB than in the NB form.[15] The latter can present, in its evolution, development radiological worsening with BQ or cavitations, almost indistinguishable from the initial BQ disease.[24] It is also considered worse prognosis the presence of spread, recurrence or resistance, and infection with *M. xenopi*.[25-27]

If we focus on host factors, it is considered poor prognosis male, elderly, and high number of comorbidities.[15] To these should be added certain radiological factors in acute although treatment with rifampicin (RF) seems to be protective.[26] In the study of Hayash *et al*.[15] published as the CLD poor prognosis clinical forms, disseminated or unclassifiable, BMI <18.5 kg/m^2 and anemia.

In short, radiological forms non-NB, being male, with advanced age, presence of comorbidities, anemia, hypoalbuminemia, BMI <18.5 kg/m^2, or erythrocyte sedimentation rate >50 mm/h are considered poor prognostic factors in disease NTM in general, while the forms CLD or CLD + NB, elevated C-reactive protein (CRP), BMI <18.5 kg/m^2 are for MAC pulmonary disease.[6] Referred to radiological deterioration of patients with MAC lung disease has found several risk factors: anemia, increase in serum albumin and CRP, or have had hemoptysis.[7]

More complicated it is to find correlation between mortality and therapeutic regimens, either two or five drugs, since it seems that those who need more drugs are those that have more risk factors.[15] For MAC, therapeutic success reaches 39%, treatment failures 27%, relapse 6%, and 17% may die (4.8% at 10 years lung disease and if evolves cavitation reaches 28.1%).[7]

TREATMENT

The evaluation of therapeutic response is based on the negative sputum culture, clinical and radiological improvement, reactivation of infection and mortality.[14]

In recent years, we have seen an evolution in the treatment employed, and from the late 1950 to 1970s, the election were isoniazid (INH), para-amino-salicylic acid and streptomycin; RF and ethambutol (EB) were used from 70 to 90, and from this date, macrolides[15] were included. Because mortality was not inconsiderable, the British Thoracic Society (BTS) conducted a clinical trial with various antibiotic regimens, observing that overall, this was about 30–40%.[28]

According to various studies, given the significant side effects of medications used for the treatment of NTM, it is recommended to keep under observation elderly, fragile and with important comorbidities patients, may in them, become

Table 1: American Thoracic Society Recommendations

	First treatment. Nodular form	First treatment. Cavitary form	Severe disease or retreatment
MAC	Claritromicina 500 mg/12h, 3 times/week Azitromicina 500/24 h, 3 times/week Etambutol 25 mg/kg weigh/24 h, 3 times/week Rifampicina 600 mg/24 h, 3 times/week	Clarithromicina 500-1,000 mg/d or azitromicina 250 mg/d Etambutol 15mg/kg/d Rifampina 450-600mg/d ±estreptomicina or amikacina	Clarithromicina 500-1,000 mg/d or azittromicina 250 mg/d Etambutol 15mg/kg/d Rifabutina 150-300 mg/d or rifampina 450-600mg/d ±estreptmicina or amikacina
M. kansasii		Rifampina 10mg/kg/d (máximo 600mg/d) Etambutol 15mg/kg/d Isoniazida 5mg/kg/d (máximo 300mg) Piridoxine 50mg/d	

Table 2: NTM lung disease care and bronchiectasis recommendatios

Screening	**1.** The potential for cross-infection of NTM (particularly *M. abscessus* complex) between individuals with CF should be minimised by following national infection control guidelines.
	2. Cultures for NTM be performed annually in spontaneously expectorating individuals with a stable clinical course.
	3. In the absence of clinical features suggestive of NTM pulmonary disease, individuals who are not capable of spontaneously producing sputum do not require screening cultures for NTM.
	4. Culture and smears for acid fast bacilli from sputum should be used for NTM screening.
	5. Oro-pharyngeal swabs should not be used for NTM screening.
Microbiology	**6.** Cultures and smears for acid fast bacilli (AFB) from sputum, induced sputum, bronchial washings or broncho-alveolar lavage samples can be used to evaluate individuals with CF suspected to have NTM pulmonary disease.
	7. Transbronchial biopsies should not be routinely used to detect NTM in individuals with CF suspected to have NTM pulmonary disease.
	8. Oro-pharyngeal swabs should not be used to perform diagnostic smears and cultures in individuals with CF suspected to have NTM pulmonary disease.
	9. Respiratory tract samples should be cultured using both solid and liquid media.
	10. The incubation duration for NTM cultures should be for a minimum of 6 weeks.
	11. An NTM culture should be processed within 24 hours of collection to optimize the detection of NTM in respiratory samples. If a delay in processing is anticipated, refrigeration of samples is advised.
	12. Respiratory tract samples should be decontaminated using the standard N-Acetyl L-cysteine NALC (0.5%) – NaOH (2%) method.
	13. If a sample remains contaminated with gram-negative bacteria after standard NALC-NaOH decontamination, it should be further treated with either 5% oxalic acid or 1% chlorhexidine.
	14. Non-culture based methods should not be used for detecting NTM in respiratory tract samples.
	15. All NTM isolates from individuals with CF should undergo molecular identification.
	16. All NTM isolates from individuals with CF should be identified to the species level, except for *M. intracellulare, M. avium and M. chimaera*, where identification can be limited to *M. avium* complex (MAC), and *M. abscessus* complex, which should be sub-speciated.
	17. For *M. avium* complex, clarithromycin susceptibility testing should be performed on an isolate recovered prior to initiation of treatment. Clarithromycin susceptibility testing should also be performed on subsequent isolates if the patient a) fails to culture convert after six months of NTM treatment; b) recultures *M. avium* complex after initial culture conversion while on NTM treatment; or c) recultures *M. avium* complex after completion of NTM treatment.
	18. For *M. abscessus* complex, susceptibility testing should include at least clarithromycin, cefoxitin and amikacin (and preferably also tigecycline, imipenem, minocycline, moxifloxacin and linezolid).
	19. Drug susceptibility testing should be performed in accordance with CLSI guidelines.
Diagnosis	**20.** ATS/IDSA criteria for the diagnosis of NTM pulmonary disease should be used in individuals with CF
	21. Other CF pathogens and co-morbidities should be considered as potential contributors to a patient's symptoms and radiological features when determining the clinical significance of NTM positive cultures.
	22. NTM treatment should be considered for individuals with CF who have ATS/IDSA defined NTM pulmonary disease.
	23. Individuals receiving azithromycin as part of their CF medical regimen who have a positive NTM culture should not continue azithromycin treatment while evaluation for NTM disease is underway as azithromycin monotherapy may lead to resistance. A macrolide agent may be included in a multi-drug treatment regimen if criteria are met for NTM disease.
Treatment	**24.** Treatment of *M. abscessus* complex pulmonary disease should involve an intensive phase followed by a continuation phase.
	25. The intensive phase should include a daily oral macrolide (preferably azithromycin) in conjunction with 3-12 weeks of intravenous amikacin and one or more of the following: intravenous tigecycline, imipenem or cefoxitin, guided but not dictated by drug susceptibility testing. The duration of intensive phase therapy should be determined by the severity of infection, the response to treatment and the tolerability of the regimen.
	26. The continuation phase should include a daily oral macrolide (preferably azithromycin) and inhaled amikacin, in conjunction with 2-3 of the following additional oral antibiotics: minocycline, clofazimine, moxifloxacin and linezolid, guided but not dictated by drug susceptibility testing.
	27. Individuals with *M. abscessus* complex pulmonary disease should be managed in collaboration with experts in the treatment of NTM and CF as drug intolerance and drug-related toxicity occur frequently and changes in antibiotic therapy are often required.
	28. Monotherapy with a macrolide or other antimicrobial should never be used in the treatment of *M. abscessus* complex pulmonary disease.
	29. The same antibiotic regimen should be used for treatment of all species within the *M. avium* complex.
	30. Clarithromycin-sensitive *M. avium* complex pulmonary disease should be treated with a daily oral antibiotic regimen containing a macrolide (preferably azithromycin), rifampin and ethambutol.
	31. Intermittent (three-times-per week) oral antibiotic therapy should not be used to treat *M. avium* complex pulmonary disease.
	32. Monotherapy with a macrolide or other antimicrobial agent should never be used in the treatment of *M. avium* complex pulmonary disease.
	33. An initial course of intravenous amikacin should be considered for the treatment of *M. avium* complex pulmonary disease in the presence of one or more of the following: i)AFB smear positive respiratory tract samples; ii) Radiological evidence of lung cavitation or severe infection; iii) Systemic signs of illness.
	34. Clarithromycin-resistant *M. avium* complex pulmonary disease should be managed in collaboration with experts in the treatment of NTM and CF.
	35. Individuals with CF receiving NTM treatment should have expectorated or induced sputum samples sent for NTM culture every 4-8 weeks throughout the entire course of treatment to assess the microbiological response.
	36. A schedule for detecting drug toxicity (including hearing loss, visual loss, renal impairment and liver function test abnormalities) should be set in place at the time of NTM treatment initiation and implemented throughout treatment based on the specific drugs prescribed.
	37. An HRCT scan of the lungs should be performed shortly before starting NTM treatment and at the end of NTM treatment to assess the radiological response.
	38. NTM antibiotic therapy should be prescribed for 12 months beyond culture conversion (defined as three consecutive negative cultures, with the time of conversion being the date of the first of the three negative cultures) as long as no positive cultures are obtained during this 12 months.
	39. Individuals who fail to culture convert despite optimal NTM therapy may benefit from long term suppressive antibiotic treatment.
	40. When amikacin is given intravenously or when streptomycin is given intravenously or intramuscularly, serum levels should be monitored and dosing adjusted to minimize ototoxicity and nephrotoxicity.
	41. Serum levels of other anti-mycobacterial drugs should not be routinely obtained. However, absorption of oral medications is often reduced in CF. Therefore use of therapeutic drug monitoring should be considered for individuals failing to improve despite taking recommended drug regimens or for those on concomitant medications with significant interactions with NTM drugs.
	42. Interferon gamma should not be used as adjuvant therapy for NTM pulmonary disease in individuals with CF.
	43. Vitamin D should be supplemented according to national CF care guidelines.
	44. Lung resection should only be considered in extraordinary circumstances and in consultation with experts in the treatment of NTM and CF.
Transplantation	**45.** All individuals with CF being considered for lung transplantation should be evaluated for NTM pulmonary disease.
	46. The presence of current or previous respiratory tract samples positive for NTM should not preclude individuals being considered for lung transplantation.
	47. Individuals with CF who have NTM pulmonary disease and are being evaluated for transplantation should commence treatment prior to transplant listing.
	48. Individuals with CF receiving NTM treatment with sequential negative cultures may be eligible for transplant listing.
	49. Individuals with CF who have completed treatment for NTM pulmonary disease with apparent eradication of the organism may be eligible for transplant listing.
	50. The presence of persistent *M. abscessus* complex or *M. avium* complex infection despite optimal therapy is not an absolute contraindication to lung transplant referral.

a chronic and incurable process, mortalities at 5 years 2% and 10 years of 9%.[4,15]

According to the clinical trial conducted by SBT, comparing to 2 years two therapeutic forms (RF + EB + clarithromycin *vs*. RF + EB + ciprofloxacin), the best results were in the regime with ciprofloxacin. Therefore, the SBT recommended to administer INH + ciprofloxacin in patients in whom treatment was <12 months.[28]

One of the main questions that we, especially when we are facing a clinically NB, is the speed of initiation of treatment. When trying to answer it, we can find different answers. Two groups were asked, one of pulmonologists and other experts in NTM, if ever actively try a new case of NTM infection. In pulmonologists respondents, 50% would try, while 37.5% would not try; however, experts answered that 79% would try and only 10% would not treat.[11] In another very recent work, faced with a similar question, <20% of American physicians and 53% of Canadians were trying NTM lung disease.[29]

As no agreements have been reached, Gochi *et al*.[7] found that if there are certain risk factors, treatment should start early. If these are not recorded, it would be indicated close monitoring of the patient.

In short, although it is reached NTM disease diagnosis, treatment indication is not always mandatory. Given the side effects, it should clearly assess the risk-benefit of therapy for each patient. First, you must have a clear understanding of the species of NTM and its association with morbidity and mortality. Second, it is considered appropriate to meet patient comorbidities, severity of the disease, its evolution, and tolerability of therapy. Finally, it is helpful to know whether BQ base was responsible for the worsening of the patient.[19] Many authors recognized that kept active observation, starting treatment if there was evidence of disease progression.[7]

Most recommendations for the treatment of disease rely NTM in treating MAC. Due to the discrepancies between *in vivo* and *in vitro*, only resistance to macrolides[27,30] is analyzed, so it is recommended to avoid monotherapy with these drugs.

In NB ways, you get to recommend a flashing three times a week therapy. In severe cases, a more aggressive therapy is needed. Dual therapy is recommended only in mild cases of NB or intolerant to treatment [Table 1]. As in CF, it is advisable to culture before starting treatment with macrolides and stop if MNT[4,31] is isolated.

With treatment negativization is achieved in 86% of cases, with little-zero resistance. Have been reported up to 48% of recurrences after treatment correctly performed, of which 75% were reinfected by a new genotype of MNT and 25% was a recovery from the previous genotype, increasing this possibility when it occurs before age 10 months after completion of treatment. Factors that may lead to a reactivation-reinfection are low BMI, FC disease, emphysema base coexistence of allergic bronchopulmonary aspergillosis, previous resistance to macrolides, and consolidations.[18,32]

Therefore, emphasis is placed on close monitoring of patients during and after treatment. It has been postulated that PET could help diagnose the therapeutic efficacy and possible relapse although much remains to recommend its use.[33]

REFLECTIONS

CF takes years ahead against other BQ, looking for similarities and differences between them. American and European societies CF have attempted to adapt the recommendations of the ATS for the treatment of NTM.[34] I think it might be advisable to carry out another adaptation for non-CF BQ; the high prevalence is reaching NTM lung disease in them [Table 2].

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Conflicts of interest

There are no conflicts of interest.

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