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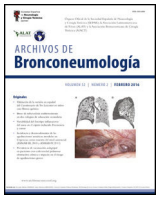

Scientific Letter

[Translated article] Non-Tuberculous Mycobacterial Diseases in Spain: Treatment and Evolution

Enfermedades por micobacterias no tuberculosas en España: tratamiento y evolución

To the Director,

The isolation of nontuberculous mycobacteria (NTMB) has increased dramatically over the past 20 years.[1,2]

Recommendations on the different therapeutic schedules and their duration are based on a review of a small number of cases of each species and experience with the better known mycobacteria, *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii*.[3] Few studies are available on which to base an evaluation of the real healthcare situation in Spain in terms of the treatments used or the outcome of these patients.[4]

Taking into account these premises, we designed this study with the objective of analyzing the treatments prescribed for the different species of NTMB in our country, and their outcomes.

This was a prospective multicenter observational study that included all patients in whom NTMB was isolated in any sample between September 2015 and November 2017 and recorded in the SEPAR National Registry database of the Integrated Tuberculosis Research Program (PII-TB). This database is accessed by username and password. Informed consent was obtained from all subjects and the study was approved by the Ethics and Research Committee of the 20 participating centers, located in 9 Spanish autonomous communities.

The following variables were analyzed: sociodemographic and anthropometric data, risk factors, disease criteria, treatment, and final outcome (cure, treatment completed, successful treatment, and relapse).

The following definitions were established:

NTMB disease: isolation of an NTMB in any sample that met the criteria recommended by the American Thoracic Society (ATS).[5]

Cured: negative culture in the last month of treatment and on at least 1 previous occasion.[6]

Treatment completed (clinical-radiological cure): treatment completed with no evidence of failure but with no record of negative culture in the last month of treatment and on at least 1 previous occasion.[6]

Treatment success: sum of cured and treatment completed.[6]

Relapse: emergence of at least 2 positive cultures with the same strain of the causative species after completion of treatment.[6]

Proportions were compared using the Chi-square test and the Fisher's 2-tailed test when the expected values were less than 5. A stepwise logistic regression analysis was performed, using successful treatment as a dependent variable. A *p*-value of less than 0.05 was considered significant.

A total of 515 patients were studied, of whom 191 (37%) met disease criteria, 172 with pulmonary disease (90%). One hundred and sixty (31%) patients had associated risk factors, the most common being bronchiectasis in 44 (8.5%), COPD in 50 (9.7%), and residual lesions in 40 (7.7%). Twelve (2.3%) had cystic fibrosis.

Of the 191, treatment was indicated in 145 (75.9%); the remaining 46 cases (24.1%) were not treated for the following reasons: clinical stability (17), comorbidities (9), advanced age and non-severe symptoms (3), patient decision (3), surgical treatment that was accepted as curative (1), or previous death (1); no reason was specified in 12.

Table 1 summarizes the different treatments, their duration, the side effects detected and the changes in treatment according to the NTMB species.

Overall, 98.7% of patients with MAC received a regimen including macrolides, 92.8% with *M. kansasii* received isoniazid, rifampicin, and ethambutol, while for *Mycobacterium abscessus*, 13 drugs were used in 13 different regimens, most frequently clarithromycin (65%), intravenous amikacin (59%), linezolid (59%), and nebulized amikacin (47%). Surgery was performed in 6 cases: 4 for MAC and 2 for *M. abscessus*.

The final outcome of the various NTMBs is reflected in Table 2. Treatment was considered successful in 123 (85%) individuals, in whom the univariate study was associated with an absence of risk factors ($p = 0.03$) and a NTMB species other than *M. abscessus* ($p = 0.04$); in the logistic regression analysis, only a lack of risk factors maintained an independent association (OR: 7.25; 95% CI: 0.93–56.44; $p = 0.04$). Relapse was observed in 13 patients (7.2%).

The decision to start treatment should be based on the clinical presentation, the causative mycobacterial species, and the patient's immune status. In our series, treatment was started in 76% of cases. In patients with MAC, this percentage was 72%, virtually all of the regimens included macrolides, and the final outcome was favorable in 82% of cases. To summarize, 91% of patients received treatment according to the various clinical guidelines.[3] This percentage, along with the percentage of treated patients, is much higher than described in a previous study, in which 55% were treated, and only 13% received an appropriate therapeutic regimen.[7]

Similar findings were observed for *M. kansasii* disease, in which an appropriate treatment regimen was established in more than 90% of cases, and the outcome was favorable in 85.7%, 75% of whom achieved cure, a finding also reflected in other studies that reported a cure rate of up to 76%.[8] In this respect, in a meta-analysis reviewing 24 studies, *M. kansasii* was the NTMB with the highest conversion rate after treatment, showing figures above 80%.[9]

The treatment of diseases caused by rapidly growing mycobacteria is significantly more complex.[10] The current recommendations for *M. abscessus* include a first phase that should include oral

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Table 1
Prescribed treatments and side effects, by species.

Species	Treatment prescribed		Duration	Side effects		Medication changes
	n	Regimen		%		%
MAC	38	Cla + R + E	>12 months	11	Gastrointestinal	18
	22	Azt + R + E		5	Cutaneous	
	4	Cla + R + E + Amg		3	Hepatic	
	3	Cla + R + E + Mxf				
	2	Cla + E + Mxf				
	1	Cla + E + St				
	1	Cla + E + Ctx				
	1	Azt + E + Ptn				
	2	Cla + Cpx				
	1	Azt + E				
	1	Azt + Rfb				
	1	Azt + Mxf				
	1	Cla				
	1	E				
M. kansasii	11	H + R + E	9–12 months	7	Fever	14
	1	H + R + E + Lfx + Cla		7	Vertigo	
	1	H + R + E + St		7	Hepatic changes	
	1	Unknown				
M. simiae	3	R + E + Azt	>12 months	13	Gastrointestinal	25
	3	R + E + Cla		13	Ocular	
	2	R + E + Cla + Mxf				
M. xenopi	1	R + Cla + Mxf + H	>12 months	17	Gastrointestinal	17
	1	R + E + Azt + Mxf				
	1	R + E + Cla + Mxf				
	1	R + E + Cla				
	2	R + E + Cla + H				
M. lentiflavum	1	Rfb + Cla + Am	>12 months	100	Digestive	0
M. gordonae						
M. szulgai	2	R + E + Cla	>12 months	0		0
M. marinum	1	R + E + Cla	>12 months	0		0
M. parascrofulaceum	1	Rfb + E + Azt	>12 months	100	Hearing loss	0
M. stomatepiae						
M. abscessus	5	Cla + Lzd + Am	4 months to 2 years	18	Gastrointestinal	41
	1	Cla + Mxf + Am		12	Neurological	
	1	Clar + Mxf + Am + Lzd + Imp		6	Anemia	
	1	Cla + Lzd + Am + Cft		6	Hearing loss	
	1	Cla + Lzd + Am + Cpx				
	1	Cla + Cpx + Imp + Am				
	1	Mxf + Lzd + Am				
	1	Tgc + Lzd + Mrp + Cfz				
	1	Mrp + Mfx + Am				
	1	Am + Cft + Tgc				
	1	Am + Imp + Tgc				
	1	Cla + Cpx				
	1	Cla + Cft + Am + Mxf				
M. fortuitum	1	Cpx + Cla + R + H	4–16 months	0		0
	1	Mxf + R + Ctx				
	1	Lfx + Am + Mrp				
	1	Lfx + Cla				
	1	Cpx + Am + R + Ctx				
	2	R + H + E				
M. chelonae	2	Cla + Cpx + R	6–12 months	13	Polyarthralgias	0
	1	Cla + Cpx				
	1	Cla + Dxc				
	1	Cla + Dxc + H				
	1	Cla + Mrp				
	1	Azt + Lfx				
	1	Azt + R + E				
M. mucogenicum						
M. smegmatis	1	Azt + R + E		0		0

Am: amikacin; Amg: aminoglycoside; Azt: azithromycin; Cft: cefoxitin; Cfz: clofazimine; Cla: clarithromycin; Cpx: ciprofloxacin; Ctx: cotrimoxazole; Dxc: doxycycline; E: ethambutol; H: isoniazid; Imp: imipenem; Lfx: levofloxacin; Lzd: linezolid; MAC: *Mycobacterium avium* complex; Mrp: meropenem; Mxf: moxifloxacin; Ptn: protionamide; R: rifampicin; Rfb: rifabutin; ST: streptomycin; Tgc: tigecycline.

and intravenous drugs and a maintenance phase with oral and nebulized drugs, which will be selected according to the susceptibility study, route of administration, progress, and tolerance. For this reason, establishing an appropriate scheme is difficult, as reflected in different studies, in which multiple antibiotics were used in combination in different regimens.[11] In another, surgical resection was necessary in 22% of cases in the face of high intolerance[12] and high toxicity rates.[13] In our series, 89% of patients completed treatment and 13 different regimens were administered with combinations of 13 different drugs. Toxicity was observed in 37% and treatment was successful in 47% (29% cured). Of particular interest are the high proportion of patients treated, which in other series did not reach 50%,[7] and the low percentage of use of clarithromycin and of cure, that was lower than that achieved in previous studies where

Table 2
Final outcome of the most frequent cases of treated NTMB.

	MAC	*M. kansasii*	*M. simiae*	*M. xenopi*	*M. lentiflavum*	*M. abscessus*	*M. fortuitum*	*M. chelonae*
Cases	110	14	8	6	5	19	10	9
Treatment	79 (72%)	14 (100%)	8 (100%)	6 (100%)	1 (20%)	17 (89%)	7 (70%)	8 (89%)
Check-up	97 (88%)	13 (93%)	8 (100%)	6 (100%)	3 (60%)	18 (95%)	10 (100%)	9 (100%)
Cured	36 (46%)	9 (64%)	2 (25%)	3 (50%)	0	5 (29%)	5 (71%)	5 (63%)
Treatment completed	29 (37%)	3 (21%)	5 (62%)	3 (50%)	0	3 (18%)	2 (29%)	2 (25%)
Treatment success	82%	86%	87%	100%	0	47%	100%	88%

MAC: *Mycobacterium avium* complex; NTMB: nontuberculous mycobacteria.

it ranged from 48[11] to 58%.[12] Difficulties with treatment are significant – response is poor and associated side effects are common – so other therapeutic options should be explored. In this regard, the use of the inhaled route seems promising, since it achieves high local concentrations, good lung tissue penetration, and fewer systemic side effects, making it potentially beneficial in all types of mycobacterial infections.[14]

Lastly, we analyzed the factors associated with the final therapeutic outcome and found that in the univariate analysis, the likelihood of treatment failure was linked with *M. abscessus* infection and the presence of risk factors, although only the latter showed an independent association. We can speculate that not only the species but also the risk factors and concomitant diseases have an impact on the final outcome.

Our study has some inherent design limitations, which make selection bias possible. However, it should be noted that one of its main strengths is that all researchers were mycobacteria experts who participate regularly in the PII-TB, and we believe this impacts positively on appropriate data collection and reduces this possibility of selection bias.

We conclude that a large number of cases of NTMB disease have been treated in our series, with a satisfactory outcome at rates similar to those previously reported, probably due to the high degree of compliance with the recommendations of the different clinical guidelines, although the presence of concomitant diseases also appears to influence the final outcome.

Appendix 1. Working Group of the Integrated Tuberculosis Research Program (PII-TB)

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