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PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Predictive factors for a one-year improvement in nontuberculous mycobacterial pulmonary disease: An 11-year retrospective and multicenter study

Gilbert Cadelis[1]*, Rodolphe Ducrot[2], Arnaud Bourdin[3,4], Nalin Rastogi[5]

1 Department of Pulmonary Medicine, University Hospital of Pointe-à-Pitre, Pointe-à-Pitre, Guadeloupe, France, **2** Department of Pulmonary Medicine, University Hospital of La Reunion, Saint Pierre, La Reunion, France, **3** Department of Respiratory Diseases, University Hospital of Montpellier, Montpellier, France, **4** PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, Montpellier, France, **5** WHO Supranational TB Reference Laboratory, Tuberculosis & Mycobacteria Unit, Institut Pasteur de la Guadeloupe, Abymes, Guadeloupe, France

* gilbert.cadelis@chu-guadeloupe.fr

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Abstract

Background

Nontuberculous mycobacterial pulmonary disease (NTM-PD) has become an emerging infectious disease and is responsible for more deaths than tuberculosis in industrialized countries. NTM-PD mortality remains high in some series reportedly ranging from 25% to 40% at five years and often due to unfavorable evolution of NTM-PD despite established treatment. The purpose of our study was to search for early factors that could predict the favorable or unfavorable evolution of NTM-PD at the first year of treatment.

Methods

In this retrospective and multicenter study, we selected 119 patients based on clinical, radiological and microbiological data from 2002 to 2012 from three French university hospitals (Guadeloupe, Martinique, Montpellier) with definite (meeting the criteria of the American Thoracic Society and the Infectious Disease Society of America in 2007; ATS/IDSA) or probable (one positive sputum culture) NTM-PD. We compared two patient groups: those who improved at one year (clinical symptoms, radiological lesions and microbiology data) and those who did not improve at one year. The data were analyzed for all patients as well as for subgroups by gender, HIV-positive patients, and *Mycobacterium avium complex* (MAC) infection.

Results

The average patient age was 50 years ± 19.4; 58% had respiratory comorbidities, 24% were HIV positive and 19% had cystic fibrosis. Coughing concerned 66% of patients and bronchiectasis concerned 45%. The most frequently isolated NTM were MAC (46%). 57% (n = 68) of patients met the ATS criteria and improved status concerned 38.6% (n = 46). The

improvement factors at one year of NTM-PD were associated with the duration of ethambutol treatment: (Odds ratio adjusted [ORa]: 2.24, 95% Confidence interval [CI]; 2.11–3.41), HIV-positive status: (ORa: 3.23, 95% CI; 1.27–8.45), and male gender: (ORa: 2.34, 95% CI; 1.26–8.16). For the group with NTM-PD due to MAC, improvement was associated with the duration of macrolide treatment (ORa: 3.27, 95% CI; 1.88–7.30) and an age <50 years (ORa: 1.88, 95% CI; 1.55–8.50).

Conclusion

In this retrospective multicenter study, improvement at one year in patients with definite or probable NTM-PD was associated with the duration of ethambutol treatment, HIV-positive status and male gender. For the group of patients infected with MAC, improvement was associated with the duration of macrolide treatment and an age <50 years. Identifying predictors of improvement at one year of NTM-PD is expected to optimize the management of the disease in its early stages.

Author summary

Early predictive factors for a favorable development of nontuberculous mycobacterial pulmonary disease (NTM-PD) are important to improve management due to the high mortality of this infection at 5 years. The purpose of this study was to search for early factors that could predict at the first year, the favorable or unfavorable evolution of NTM-PD. This multicenter and retrospective study shows the importance of the duration of use of certain antibiotics (e.g. ethambutol and macrolides) in combination with other drugs in the one-year improvement of patients with NTM-PD. It also confirms the favorable prognosis at one year of NTM-PD patients with HIV-positive status. Identifying predictors of improvement at one year of NTM-PD is expected to optimize prognosis of the disease in its early stages.

Introduction

Infection with nontuberculous mycobacteria (NTM) preferentially affects the lungs and occurs by inhalation of aerosols containing mycobacteria [1, 2]. NTM are ubiquitous environmental bacteria found in soil, but also in other sources such as contaminated water taps. The frequency of NTM species can vary from region to region in the world [1, 3]. NTM pulmonary disease (NTM-PD) has today become an emerging infectious disease in industrialized countries. Its increasing prevalence is estimated at more than 50 cases per 100,000 persons in some demographic groups in the US [4]; while its incidence in Europe ranges from 0.2 to 2.9 / 100,000 inhabitants [1]. Remarkably, all NTM species are not likely to cause NTM-PD; only a few species such as *Mycobacterium avium complex* (MAC), *M. abscessus*, *M. xenopi* and *M. kansasii* are frequently involved [5]. Indeed, the clinical relevance of NTM differs by species since they are not endowed with the same virulence [6].

The diagnostic criteria of the American Thoracic Society and the Infectious Disease Society of America in 2007 (ATS/IDSA) [7] have established the diagnosis of NTM-PD based on clinical symptoms, radiological lesions and microbiology data. During this decade, real progress has been made in the understanding of this disease [4]. We know for example that besides

immunosuppression by HIV or cystic fibrosis, NTM-PD occurs in lungs whose architecture is already weakened by chronic respiratory diseases such as primarily chronic obstructive pulmonary disease (COPD) and bronchiectasis [1, 5]. The establishment of NTM-PD in impaired lungs can cause the destruction of the pulmonary parenchyma [8] and eventually lead to death due to the evolution of NTM-PD [9]. Patients with NTM-PD are not all treated because current treatments are often long, expensive and not without side effects [10]. NTM-PD mortality remains high in some series ranging from 25% to 40% at five years [1, 9, 11]. The main factors of poor outcomes identified in mortality studies at five years corresponded to an advanced age, the existence of respiratory comorbidities, radiological cavity lesions, and some mycobacteria such as *M. xenopi* [11,12,13].

Given the deteriorating respiratory status of patients due to the evolution of NTM-PD despite established treatment and the relatively high mortality at five years, it seemed important to search for early factors that could predict from the first year the favorable or unfavorable evolution of NTM-PD, and thus improve prognosis. Hence, the main purpose of this study was to identify factors that contribute to the clinical, radiological and microbiological improvement at one year of a cohort of 119 patients with definite (meeting the criteria ATS/IDSA) or probable (one positive sputum culture) NTM-PD, regardless of their immune status or their respiratory history. The secondary goal of this study was to report for the first time, a clinical, radiological and microbiological description of NTM-PD in a population of Afro-Caribbean patients in the French West-Indies.

Materials and methods

Ethics statement

This observational study received approval from the Institutional Review Board of the French learned society for respiratory medicine (Société de Pneumologie de Langue Française; No: 2015–003). All the participants gave their written consent. The parents/guardians provided written informed consent on behalf of participants below 18 years of age.

This study was carried out in accordance with the principles of the Helsinki Declaration.

Study design and patient selection

This study was a retrospective, multicentric, observational study over a 11-year period between 2002 and 2012 in three French university hospitals (CHU), two of which are located in the French West-Indies (University Hospital of Fort de France, Martinique; and University Hospital of Pointe-à-Pitre, Guadeloupe), and the 3rd in Metropolitan France (University Hospital of Montpellier, France). From the computerized databases of the bacteriological laboratories of these three institutions, we searched all patients over 13 years old with at least one positive culture for NTM between 2002 and 2012. A total of 119 patients were therefore finally retained for this study regardless of their immune status. The exclusion criteria were an age below 13 years and the absence of patient consent.

Data collected

Patient data. Age, sex, place of residence, tobacco and alcohol consumption, history of respiratory disease, diabetes, the presence of known gastroesophageal reflux disease, usual medications, HIV-positive serology, and taking immunosuppressants were recorded.

Clinical and radiographic data. NTM discovery mode, respiratory symptoms and general symptoms at diagnosis. The main thoracic radiographic abnormalities: cavities in the pulmonary parenchyma, presence or absence of solitary pulmonary nodules (>1 cm),

bronchiectasis with or without micronodules, alveolar condensations, mediastinal lymph nodes (>1 cm) and pleural effusion. All patients had a thorax X-ray and chest CT scans interpreted by two radiologists specialized in thoracic imaging.

Bacteriological data. The sources of bacteriological samples (sputum, bronchoalveolar lavage, pleural fluids, blood cultures and surgical samples), the *Mycobacterium* species and the number of positive bacteriological culture samples were recorded. The bacteriological laboratories of the three institutions involved in the study have specialized units referenced nationally for NTM. For each patient in the study, we determined those who met the ATS/IDSA diagnostic criteria [7] for NTM-PD on the evaluation of clinical, radiological and microbiological criteria and the exclusion of other diagnoses (tuberculosis, cancer, histoplasmosis, etc.). ATS/IDSA 2007 microbiological criteria [7] are defined by the presence of at least two positive bacteriological culture samples from a non-sterile site, or at least one positive bacteriological culture sample from a sterile site.

In our series, NTM-PD was distinguished by two patient categories: those who completely met the diagnostic criteria of pulmonary disease defined by the ATS/IDSA and therefore had definite NTM-PD and those who did not meet the criteria because they had one positive sputum culture for NTM, which corresponded to probable NTM-PD cases, only meeting the ATS/IDSA clinical and radiological criteria for NTM-PD.

Therapeutic data. We recorded if the patient was treated or not, the type of antibiotic molecules used, combinations of therapeutic molecules, the total duration of antibiotic treatment and the treatment side effects. The therapeutic management and monitoring of patients were decided by clinicians of the three institutions in consultation with the National Mycobacteria Reference Center. The clinician in charge implemented the treatments and the follow-up of the patient that were commonly initiated in the hospital, either in hospital itself or the outpatient department depending on the clinical condition of the patient. All treated patients received a therapeutic combination.The therapeutic combinations initially proposed to the patients per NTM species isolated are summarized in S1 Table.

Patient follow-up. Patient follow-up was noted from the medical records. This follow-up consisted of scheduling a consultation every 2–3 months until culture negativity, and was followed three times a year throughout the duration of treatment. In the follow-up visits, there was a check of treatment adherence and eventual side effects, as well as obtaining bacteriological samples and thoracic imaging, if deemed necessary. Nonetheless, in all cases the patients benefited from a thoracic CT scan at varying frequencies during their follow-up.

Patient outcome at one year. The disappearance or persistence of clinical symptoms at diagnosis, changes in thoracic imaging (regression or disappearance of the initial lesions), negative or positive bacteriological samples, death and discovery of another disease during follow-up were recorded.

Primary evaluation criteria

This was a composite endpoint defined by the disappearance at one year of respiratory symptoms and/or initial symptoms, regression or normalization at one year of the initial radiological lesions, and negative bacteriological cultures at one year. Negative bacteriological cultures were defined as at least three consecutive negative respiratory culture specimens at the end of one year. Patients were classified as having an improved status at one year only if all the three criteria were met (vs. unimproved status if this was not the case).

Statistical analysis

Statistical analyses were designed to determine the parameters related to the primary endpoint, i.e., an improved status at one year. Univariate analysis was first conducted to study the independent variables related to the primary endpoint. Statistical tests used for categorical variables were the Chi-squared test or the Fisher exact test and for quantitative variables, the Student's t-test or the Wilcoxon-Mann-Whitney test. For all statistical tests, the significance level was set at 5% and a power >90%.

Independent variables with a p-value less than 0.2 determined by univariate analysis were retained for the multivariate model. Multivariate analysis consisted of logistic regression analysis. The dependent variable was the binary variable (improved / unimproved status); independent variables were introduced into the model using a backward regression approach. Variables with a p-value less than 0.05 were selected. The results were produced as odds ratios with 95% confidence intervals.

The choice of multivariate logistic regression was dictated:

- By the characteristics of the variables to be studied. The dependent variable was binary and was used to separate two groups of individuals: those who improved according to the main criterion and those who did not improve. The explanatory variables were both quantitative and qualitative.

- By the study objective, which was to search for factors and their weight among the adjusted variables (adjusted odds ratio) that could influence the variable to be explained while adjusting for the confounding factors.

A subgroup analysis was performed for the population infected by MAC for the HIV-positive population and by gender.

Processing and statistical analysis were performed using version 3.3.2 of the R software. The libraries used in the statistical analysis with R included: base-package, stats-package, BioStatR-package, MASS-package and pwr-package.

Results

General characteristics of NTM-PD patients with improved and unimproved status (Table 1)

Patients with an improved status represented 38.6% (n = 46). The regression of clinical symptoms at one year concerned 56.3% (67/119), the disappearance or regression of radiological lesions at one year concerned 38.6% (46/119) of patients and negative bacteriological cultures at one year were obtained for 51.2% (61/119). A statistically significant difference was revealed between the two groups for age ($p<0.05$), place of residence ($p<0.01$) and the percentage of patients with HIV-positive serology ($p<0.02$).

No difference was found between the two groups for the ATS/IDSA diagnostic criteria (58.6% vs. 56.1%, p = 0.93).

Clinical and radiological characteristics of NTM-PD patients with improved and unimproved status (Table 2)

A statistically significant difference was found between the two groups (improved / unimproved status) in the circumstances of the disease discovery ($p<0.006$). There was no statistically significant difference between the two groups in terms of initial respiratory symptoms and initial radiological lesions.

Table 1. The general characteristics of patients with improved versus unimproved status at one year.

	Total patients N = 119 (%)	Patients with improved status n = 46 (38.6%)	Patients with unimproved status n = 73 (61.3%)	P value
Age (mean ± SD),years	50.4 ±-19.4	46.1 ±19.0	55.0 ±20.1	0.05
Sex				0.06
Male	80(67.2)	36 (78.2)	44 (60.2)	
Female	39(32.7)	10 (21.7)	29 (39.7)	
Place of residence				0.01
Guadeloupe (West Indies)	56(47.0)	27 (58.6)	29 (39.7)	
Martinique (West Indies)	19(15.9)	2 (4.3)	17(23.2)	
Montpellier (France)	44(36.9)	17 (36.9)	27 (36.9)	
Respiratory history				0.17
yes	70(58.8)	23 (50.0)	47 (64.3)	
No	49(41.1)	23 (50.0)	26 (35.6)	
Respiratory disease				0.27
-Cystic fibrosis	23(19.3)	11 (23.9)	12 (16.4)	
-Bronchiectasis	23(19.3)	7 (15.2)	16 (21.9)	
-Chronic obstructive pulmonary disease	18(15.1)	2 (4.3)	16 (21.9)	
-Lung fibrosis	2(1.6)	0 (0.0)	2 (2.7)	
-Asthma	2(1.6)	2 (4.3)	0 (0.0)	
-previous history of tuberculosis	3(2.5)	2(4.3)	1 (1.3)	
-kyphoscoliosis	1 (0.8)	1 (2.1)	0 (0.0)	
-Sarcoidosis	1 (0.8)	0 (0.0)	1 (1.3)	
Immunosuppressive therapy	10(8.4)	2 (4.3)	8 (10.9)	0.36
HIV serology positive	29(24.4)	17(36.9)	12(16.4)	0.02
CD4<200/mm3	23(19.3)	14(30.4)	9(12.3)	0.02
Diabetes	17(14.3)	7(15.2)	10(13.6)	0.66
Gastroesophageal reflux	15(12.6)	7 (15.2)	8 (10.9)	0.30
Smoking	38(31.9)	12 (26.0)	26(35.6)	0.46
Alcoholism	22(18.5)	12(26.0)	10(13.6)	0.14
ATS/IDSA criteria	68(57.1)	27(58.6)	41(56.1)	0.93

Improved status at 1-year: Patients improved clinically and radiological and their microbiological samples were negative. **Unimproved status at 1-year**: The patients did not improve their clinical state or their radiological lesions or their microbiological samples did not negative.

ATS/IDSA criteria: American Thoracic Society and the Infectious Disease Society of America

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Bacteriological characteristics of NTM-PD patients with improved and unimproved status (Table 3)

In Guadeloupe, the main NTM encountered in decreasing order were MAC, *M*. *simiae* and *M*. *fortuitum*, in Martinique, *M*. *fortuitum* followed by MAC, then M. *gordonae*; and in Montpellier, MAC then *M*. *abscessus* complex, followed by *M*. *xenopi*. No statistically significant difference was found between the improved / unimproved status groups for the mycobacterial species. The ATS/IDSA criteria were met for 62% of patients with MAC, 82% with *M*. *abscessus*, 50% with *M*. *fortuitum* and 45% with *M*. *simiae*. For bacteriological samples, 76% met the ATS/IDSA microbiological criteria. There was no statistically significant difference between the two groups for the ATS/IDSA microbiological criteria. The positive predictive value (PPV) of the ATS/IDSA microbiological criteria for definite NTM-PD was 89% (68/76) CI 95%

Table 2. Clinical and radiological characteristics of patients enrolled.

	Total patients N = 119 (%)	Patients with improved status N = 46 (38.6%)	Patients with unimproved status n = 73 (60.3%)	P value
Circumstances of discovery				0.006
Respiratory symptoms	40 (33.6)	18 (39.1)	22 (30.1)	
Alteration of general state	20 (16.8)	11 (23.9)	9 (12.3)	
Hemoptysis	15 (12.6)	10 (21.7)	5 (6.8)	
Systematic review	14 (11.7)	10 (21.7)	4 (5.4)	
Hyperthermia	14 (11.7)	7 (15.2)	7 (9.5)	
Radiologic abnormalities	11 (9.2)	8(17.3)	3 (4.1)	
Extra-pulmonary signs	5 (4.2)			
Skin lesions		2 (4.3)	1 (1.3)	
Cervical abscess		1(2.1)	0(0.0)	
Paraspinal abscess		1(2.1)	0(0.0)	
Symptoms at diagnosis				
Cough	79 (66.4)	32 (69.5)	47 (64.3)	0.59
Sputum	61 (51.3)	24 (52.1)	37 (50.6)	0.60
Weight loss	60 (50.4)	26 (56.5)	34 (46.5)	0.52
Asthenia	55 (46.3)	26 (56.5)	29 (39.7)	0.32
Hyperthermia	43 (36.1)	15 (32.6)	28(38.3)	0.66
Dyspnea	48 (40.3)	15 (32.6)	33 (45.2)	0.47
Hemoptysis	22 (18.5)	9 (19.5)	13 (17.8)	0.67
Radiological pattern				
Bronchiectasis	54 (45.4)	19 (41.3)	35 (47.9)	0.73
Nodular opacities (>1cm)	24 (20.1)	6 (13.0)	18 (24.6)	0.24
Cavities	26 (21.8)	8 (17.3)	18 (24.6)	0.50
Consolidation	45 (37.8)	18 (39.1)	27 (36.9)	0.54
Mediastinal lymphadenopathy (>1cm)	31 (26.1)	10 (21.7)	21 (28.7)	0.54
Pleural effusion	14 (11.8)	6 (13.0)	8 (10.9)	0.77

Improved status at 1-year: Patients improved clinically and radiological and their microbiological samples were negative. **Unimproved status at 1-year**: The patients did not improve their clinical state or their radiological lesions or their microbiological samples did not negative.

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(83%-94%). Lastly, patients who did not meet the ATS microbiological had a four-fold increased risk of death at one year (OR = 4.01, 95% CI; 1.40–14.51, p<0.01).

Treatment characteristics (molecules and duration of treatment) received by NTM-PD patients with improved and unimproved status and patient outcomes (Table 4)

No statistically significant difference was found between the two groups for treated patients, as well as in the total duration of treatment. There was a statistically significant difference in the duration of ethambutol treatment between the two groups (p<0.001, effect size: 0.81, power: 0.99). Side effects related to treatment concerned 10 of 63 patients (15.8%), five had minor side effects (digestive disorders) and five had major side effects (three cases of drug-induced hepatitis, one case of eye damage and a kidney failure). These 5 patients with major side effects had to stop their therapy. No patient in our cohort benefited from associated surgical treatment.

There was a statistically significant association between the absence of negative cultures and mortality at one year (p<0.001). The conversion rate of bacterial cultures was 60% (33/55) for

Table 3. Bacteriological characteristics of the patients.

	Total Patients n = 119	Patients with improved status n = 46 (38.6%)	Percentage of patients treated and improved (%)	Patients with unimproved status n = 73(61.3%)	P Value
Mycobacterium species					0.25
M. avium complex	55 (46.2)	26 (56.5)	53 (18/34)	29 (39.7)	
M. abscessus complex	17 (14.3)	5(10.8)	45 (5/11)	12 (16.4)	
M. fortuitum	16 (13.4)	4 (8.6)	33 (1/3)	12 (16.4)	
M. simiae	11 (9.2)	7 (15.2)	80 (4/5)	4 (5.4)	
M. gordonae	8 (6.7)	3 (6.5)	66 (2/3)	5 (6.8)	
M. kansasii	5 (4.2)	1 (2.1)	20 (1/4)	4(5.4)	
M. xenopi	3 (2.5)	3 (6.5)	100 (3/3)	0 (0.0)	
M. chelonae	1 (0.8)	1 (2.1)	100 (1/1))	0 (0.0)	
M. gilvum	1 (0.8)	1 (2.1)	100 (1/1)	0 (0.0)	
M. szulgai	1 (0.8)	0 (0.0)	0 (0/1)	1 (1.3)	
M. genavense	1 (0.8)	1 (2.1)	100 (1/1)	0 (0.0)	
Source of positive culture:					
-1 positive sputum culture	43 (36.1)	16 (34.7)		27 (36.9)	0.11
->2 positive sputum cultures	41 (34.4)	14 (30.4)		27 (36.9)	0.70
-Bronchoalveolar lavage culture	19 (15.9)	10 (21.7)		9 (12.3)	0.31
-Lung biopsy + sputum culture +	8 (6.7)	3 (6.5)		5 (6.8)	0.10
-Blood culture	7 (5.8)	3 (6.5)		4 (5.4)	0.11
-Pleural effusion culture	1 (0.8)	0		1 (1.3)	0.39
-ATS /IDSA microbiologic criteria*	76 (63.9)	30 (65.2)		46 (63.0	0.96

Improved status at 1-year: Patients improved clinically and radiological and their microbiological samples were negative. **Unimproved status at 1-year**: The patients did not improve their clinical state or their radiological lesions or their microbiological samples did not negative. **The P Value** results from the comparison between these two groups (Improved/unimproved)

ATS/IDSA: American Thoracic Society and the Infectious Disease Society of America

Percentage of patients treated and improved = number of patients treated and improved for the species / all patients treated for the same species

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MAC, 35% (6/17) for *M. abscessus complex*, 37% (6/16) for *M. fortuitum* and 72% (8/11) for *M. simiae*.

The total number of mortalities at one year was 14.2% (n = 17), all belonging to the unimproved group. The average age of deceased patients (13 men and four women) was 60 years ±12.7. We recorded 52% tobacco smokers, and 44% COPD, 29% HIV-positive and 5% cystic fibrosis patients. NTM of deceased patients were MAC (9/17; 52.9%), *M. abscessus complex* (4/17; 23.5%), *M. kansasii* (2/5; 40%) and *M. fortuitum* (2/16; 12.5%). Eight patients died of unfavorable NTM-PD evolution, one patient from pulmonary embolism and two patients from COPD exacerbations. An association between the mortality rate and mycobacterial species in the study (p = 0.86) was not found.

Factors associated with NTM-PD patient improvement at one year by multivariate analysis (Table 5)

Factors associated with an improvement at one year were the male gender (OR = 2.34), HIV-positive serology (OR = 3.23) and duration of ethambutol treatment (OR = 2.24). For the

Table 4. Therapeutic characteristics of the patients.

	Total patients n = 119 (%)	Patients with improved status n = 46 (38.6%)	Patients with unimproved status n = 73 (61.3%) n =	P value
Patients treated				0.19
Yes	63 (52.9)	30 (65.2)	33 (45.2)	
No	56 (47.1)	16(34.7)	40 (54.7)	
Duration of treatment (months)	9.1 ±6,0	10.6 ± 5.8	8.5 ± 6.3	0.10
Macrolides (Clarithromycin or Azithromycin)		6.4± 6.2	4.5 ± 4.6	0.25
Ethambutol		6.0 ±5.9	2.46 ±2.8	0.001
Rifampicin		5.6 ± 5.9	4.1 ± 3.5	0.34
Isoniazid		3.5 ±4.8	3.1 ± 4.3	0.93
Moxifloxacin		1.9 ± 4.2	1.2 ±3.5	0.83
Rifabutin		1.9 ± 3.9	1.1 ± 2.6	0.38
Pyrazinamide		0.7 ±1.1	1.7 ± 3.1	0.21
Aminoglycoside (Amikacin)		1.2 ±1.8	0.9 ±1.8	0.78
Meropenem		0.3±1.2	0.7 ± 1.6	0.25
Negative cultures at one year	61 (51.2)	46(100)	15(20.5)	0.001
Patient outcome				
One-year mortality	17 (14.2)	0.0 (0)	17 (23.2)	0.001

Improved status at 1-year: Patients improved clinically and radiological and their microbiological samples were negative. **Unimproved status at 1-year**: The patients did not improve their clinical state or their radiological lesions or their microbiological samples did not negative.

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Table 5. Factors associated with improved status at one year, multivariate analysis.

Variables	Odds Ratio	confidence interval at 95%	*P value*
For all patients (n = 119)			
HIV positive	3.23	1.27–8.45	0.01
Male	2.34	1.26–8.16	0.02
Duration of the treatment by Ethambutol (months)	2.24	2.11–3.41	0.001
For non–HIV-positive patients (n = 90)			
Male	3.54	1.12–14.0	0.04
Duration of the treatment by Ethambutol (months)	1.90	1.50–3.50	0.001
For patients with complete ATS/IDSA criteria (n = 68)			
Duration of the treatment by Ethambutol (months)	2.45	1.82–7.45	0.01
For non-HIV-positive patients with complete ATS/IDSA criteria (n = 55)			
Duration of the treatment by Ethambutol (months)	1.85	1.55–6.53	0.001
For patients with MAC (n = 55)			
Age <50ans	1.88	1.55–8.50	0.02
Duration of the treatment by Macrolide (months)	3.27	1.88–7.30	0.003
For non-HIV positive patients with MAC (n = 38)			
Duration of the treatment by Macrolide (months)	2.88	2.15–8.56	0.007

ATS/IDSA: American Thoracic Society and the Infectious Disease Society of America

MAC: Mycobacterium *avium* complex

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population meeting the ATS/IDSA diagnostic criteria, the factor associated with improvement was the duration of ethambutol treatment (OR = 2.45). For the group of patients infected by MAC, improvement factors were associated with age under 50 years (OR = 1.88) and duration of macrolide treatment (OR = 3.27).

For the group of non HIV-positive patients, improvement factors were associated with Male (OR = 3.54) and duration of ethambutol treatment (OR = 1.90).

Characteristics and outcome of NTM-PD study patients infected with MAC and *M. kansasii*

- Patient group with MAC (S2 Table): Patients infected with MAC represented 46% of our sample. Cavity forms mainly concerned men (8/40; 20%). Bronchiectasis concerned 93% (14/15) of women. Deaths at one year concerned men only at 22% (9/40), eight with cavity lesions. Men smoked and had a more pronounced respiratory history than women. A statistically significant difference was found between the group of improved and unimproved patients for age ($p<0.04$), total treatment duration ($p<0.04$), duration of macrolide treatment ($p<0.04$, effect size: 0.94, power: 0.92), negative bacteriological cultures at one year ($p<0.001$) and death at one year ($p<0.001$).
- NTM-PD patient group with *M. kansasii* (n = 5): This group of patients had a significant mortality rate (40%; n = 2/5). The average age was 50 years with four males and one female. From the patient history, two patients were monitored for pulmonary fibrosis and two patients had HIV-positive serology with a CD4 count <50. Radiology revealed 3/5 patients (60%) with cavities.

General characteristics, treatment and outcome of the NTM-PD and HIV-positive patients in the study (S3 Table)

A total of 29 patients were included. The CD4 count was below 200 for 23 patients (79%). The discovery of NTM revealed an HIV-positive status for 98% of patients. The most frequently found species was MAC (58%). A statistically significant difference between the two groups (improved / unimproved status) was found for age ($p<0.04$), percentage of treated patients ($p<0.04$), negative bacteriological cultures at one year ($p<0.001$), and percentage of deaths at one year ($p<0.04$).

Sixteen of the 29 HIV–positive patients (55%) were treated. The percentage of patients improved on treatment was 81% (13/16).

General characteristics, treatment, and outcome of NTM-PD patients in the study analyzed by gender (S4 Table)

A statistically significant difference was found between men and women for age ($p<0.04$), chronic respiratory diseases (cystic fibrosis, COPD and bronchiectasis; $p<0.004$), the incidence of sputum for women ($p< 0.02$), the type of radiological lesions and improved status at one year ($p<004$) in favor of men.

Discussion

In this work, HIV infection, treatment duration with ethambutol in combination with other antibiotic molecules, and the male gender were independent factors associated with a favorable outcome at one year of definite or probable NTM-PD. The composite endpoint adopted in our study could have a prognostic value as it effectively allows to discriminate patients who

survived at one year from those who did not. When clinical symptoms, radiological lesions and negative microbiology data were observed in function of patient outcome at one year, only the absence of negative cultures was associated with death.

The diagnostic criteria for NTM-PD proposed by the ATS/IDSA were not associated with an improved status in our study. These results were similar to those found by other authors [11,14] on the relationships between ATS/IDSA diagnostic criteria and patient prognosis. In our study, the ATS/IDSA microbiological criteria had an excellent PPV of 89% for definite NTM-PD. Winthrop et al. [15] reported a PPV of 86% for NTM-PD. Jankovics et al. [16] showed that the PPV for NTM-PD varied from 64% to 94% depending on the clinical relevance of the NTM.

The majority of NTM-PD patients in this study (52%) were from the French West-Indies. In Guadeloupe, the species that predominated among these patients was MAC (45%), while in Martinique, it was *M. fortuitum* (47%). These frequencies are in agreement with Streit et al. [17] based on an epidemiological study in Guadeloupe, Martinique and French Guiana. Likewise, NTM-PD isolates from Montpellier showed a predominance of MAC (57%) followed by *M. abscessus* (32%), which paralleled NTM epidemiology in metropolitan France [18]. Finally, NTM-PD patients with *M. abscessus* in our study met more often the ATS/IDSA criteria for pulmonary disease (82%) than patients with MAC (62%). It should however be underlined that clinical characteristics and outcomes for the cohort with MAC were not further categorized by genetic sequencing to discriminate with distinct MAC species as reported recently [19], hence not allowing to conclude on a possible variability as regards to ATS/IDSA criteria for pulmonary disease depending on infection with *M. avium*, *M. intracellulare*, *M. chimaera*, or other MAC species.

In our study, no association between improved status and NTM species could be distinguished at one year. Indeed, the relatively shorter observation period in our study may not have allowed to perceive a species dependent association; e.g., Andrejack et al. [11] did not find significant differences in mortality based on the mycobacterial species in the first year of their study, although *M. xenopi* was associated with increased mortality as compared to MAC at the longer term. In this respect, mortality due to *M. kansasii* in our study (40%) seemed high as compared to published data [20], although our cohort (n = 5) was too small to draw conclusions. Furthermore, these patients had significant comorbidities, cavity lesions (3/5) and poor prognosis [12]. For NTM-PD with MAC, two conventional radiological presentations were the cavity radiological form that preferentially affected male smokers with a respiratory history, poor prognosis at one year, and bronchiectasis in women with no deaths at one year [12, 21]. The age <50 years and duration of macrolide treatment was associated with an improvement at one year. Advanced age was reported to be a poor prognostic factor [11,12].

Macrolides are an essential treatment of NTM-PD due to MAC [1, 4, 22]. In our group with MAC, the duration of macrolide treatment was predictive of an improvement at one year. Macrolide pharmacodynamics could explain the more effective action of these molecules over time; it was shown that the maximum eradication kinetics of MAC was slow with clarithromycin compared to amikacin [23]. Hence our observation that the duration of macrolide treatment was an improvement factor at one year for NTM-PD due to MAC was not unexpected, nonetheless it remarkably corroborates the positive effect of the duration of macrolide treatment in a clinical study. Significantly, the duration of ethambutol treatment in combination with other molecules in our study emerged as an independent factor of NTM-PD improvement at one year. Although the current treatment of NTM is largely empiric [24], ethambutol, an inhibitor of arabinogalactan synthesis, is known to significantly boost *M. avium* drug susceptibility in vitro [25], and was shown to enhance activity both of clarithromycin and rifampin against MAC in extra- and intracellular assays at serum level concentrations [26]. Indeed,

the tripartite cell-envelope architecture of *M. avium* [27], is partially responsible for exclusion of antimicrobial agents, leading to its observed multiple drug resistance [28, 29]. With regard to the *M. avium* lipid bilayer at the surface of the cell-wall skeleton which decreases the permeability for hydrophilic molecules, ethambutol acts by decomposing not only the skeleton but also the lipid layer, thereby facilitating the diffusion of antibiotics [30]. These observations corroborate our main hypothesis that more the action of ethambutol is maintained over time, more the antibiotics are able to access and concentrate intracellularly with higher concentrations in the bacterium. This assumption is further substantiated by observations on synergistic effects of ethambutol with several molecules with intracellular action: rifampin, quinolones and macrolides [31, 32]. Undeniably, ethambutol is an important component in the current multidrug regimens for treatment of patients with MAC lung disease [7, 33, 34]; the microbiological response being significantly related to the duration of its use [35].

In our study, an HIV-positive status was an independent factor in improving NTM-PD at one year. Other studies have shown a dramatic improvement in HIV-positive patients with NTM-PD due to immune restoration by anti-HIV therapies [36]. Restoration of immunity, monitoring of these patients in specialized structures and treatment of NTM-PD have played an important role in improving prognosis.

Men with NTM-PD have been reported as having a worse prognosis in terms of mortality than women [11, 12]. In our study, men showed greater improvement at one year than women. The men were younger and sputum was more common among women (79% vs. 37%), as was bronchiectasis (64% vs. 36%). There was no difference between the sexes on the negativity of bacteriological cultures. Women showed little improvement clinically and radiologically compared to men due to the persistence of clinical symptoms. However, mortality at one year remained higher in men.

The strengths of our study are based on its multicenter approach, subgroup analyses and a large cohort constituted by the analysis of clinical and radiological records of patients rather than on discharge data. However, the limitations of this study are its retrospective design and the short observation period (one year), which does not allow to know if the improvement observed will persist over time. Another limitation of this study is the inclusion of probable cases of NTM-PD, which nonetheless translates a reality faced by clinicians. However, the current diagnostic criteria for NTM-PD does not have perfect sensitivity and specificity [37], and a fraction of these probable cases may evolve during monitoring to definite cases, although there is no data to confirm this assumption. Furthermore, at times one cannot conclude definitely, for example for the HIV subgroup, since the numbers in each sample (improved / unimproved) were too small to be able to carry out a multivariate analysis.

Conclusions

In this retrospective multicenter study, improvement at one year in patients with definite or probable NTM-PD was associated with the duration of ethambutol treatment, HIV-positive status and male gender. For the group of patients infected with MAC, improvement was associated with the duration of macrolide treatment and an age <50 years. Identifying predictors of improvement at one year of NTM-PD is expected to optimize the management of the disease in its early stages.

Supporting information

S1 Table. Treatment of nontuberculous mycobacterial pulmonary disease (NTM-PD).
(DOCX)

S2 Table. The general characteristics and treatment outcome of patients infected with *Mycobacterium avium* complex (MAC).
(DOCX)

S3 Table. The general characteristics and treatment outcome of patients with positive HIV-serology.
(DOCX)

S4 Table. General characteristics and treatment outcomes analyzed by gender (Male/Female).
(DOCX)

S5 Table. STROBE statement.
(DOC)

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Author Contributions

Conceptualization: Gilbert Cadelis, Rodolphe Ducrot, Arnaud Bourdin, Nalin Rastogi.

Data curation: Gilbert Cadelis, Rodolphe Ducrot, Arnaud Bourdin, Nalin Rastogi.

Formal analysis: Gilbert Cadelis, Rodolphe Ducrot, Arnaud Bourdin, Nalin Rastogi.

Methodology: Gilbert Cadelis, Arnaud Bourdin, Nalin Rastogi.

Validation: Gilbert Cadelis, Rodolphe Ducrot, Arnaud Bourdin, Nalin Rastogi.

Visualization: Gilbert Cadelis, Rodolphe Ducrot, Arnaud Bourdin, Nalin Rastogi.

Writing – original draft: Gilbert Cadelis.

Writing – review & editing: Gilbert Cadelis, Rodolphe Ducrot, Arnaud Bourdin, Nalin Rastogi.

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S1 table. Treatment of non-tuberculous mycobacterial pulmonary disease (NTM-PD)

Mycobacteria	Therapeutic regimen usually used in this study
M. avium Complex	3 drugs Per os (P.O.) :clarithromycin , rifampicin, ethambutol
M. abscessus complex	Intensive phase : clarithromycin, (in absence of inducible macrolide resistance) , amikacin plus imipenem , continuation phase : 3 drugs Per os (P.O.) : clarithromycin, (in absence of inducible macrolide resistance) + ciprofloxacin and linezolid
M. kansasii	3 drugs Per os (P.O.) : rifampicin, ethambutol, isoniazid
M. xenopi	3 drugs Per os (P.O.) : clarithromycin, rifampicin, ethambutol
M. simiae	Amikacin (intensive case only) and 2 drugs Per os (P.O.) : clarithromycin, trimethoprim/sulfamethoxazole

Drugs for a Therapeutic regimen should be based on drugs susceptibility testing results

S2 table. The general characteristics and treatment outcome of patients infected with *Mycobacterium avium* complex (MAC).

Mycobacterial Species = *Mycobacterium avium complex (MAC)*	Total patients n=55 (%)	Patients with Improved status n =26 (47.2%)	Patients with unimproved status n=29(52.7%)	P value
Age (mean ± SD),years	50.0 ±-20	42.8 ±19.6	56.4 ±18.4	0.04
Sex				0.33
Male	40(72.7)	21 (80.7)	19 (65.5)	
Female	15(27.2)	5 (19.2)	10 (34.4)	
Respiratory history				0.75
Yes	34(61.8)	15(57.6)	19 (65.5)	
No	21(38.1)	11 (42.3)	10 (34.4)	
Respiratory disease				0.27
- Cystic fibrosis	11(20.0)	8 (30.7)	3(10.3)	
- Bronchiectasis	14(25.4)	5 (19.2)	9 (31.0	
- Chronic obstructive pulmonary disease	9(16.3)	2 (7.6)	7 (24.1)	
HIV patients	17(30.9)	11(42.3)	6(20.6)	0.10
Respiratory symptoms				
Cough	31(56.3)	16(61.5)	15(51.7)	0.35
Sputum	31(56.3)	14(53.8)	17(58.6)	0.81
Radiology results				
Bronchiectasis	31(56.3)	14 (53.8)	17 (44.8)	0.80
Nodular opacities	14(25.4)	5 (19.2)	9(31.0)	0.55
cavities	9(16.3)	3(11.0)	6(20.6)	0.49
ATS/ IDSA criteria	34(61.8)	17(65.3)	17(58.6)	0.83
Treatment	34 (61.8)	18(69.2)	16 (55.1)	0.66
Duration of treatment (month)	8.4 ±5.9	7.5 ±6.9	6.2±3.6	0.06
Clarithromycin (months)		9.6 ±6.8	4.6±3..8	0.02
Rifampin (months)		5.9 ±6.4	4.6±3.2	0.25
Ethambutol (months)		5.7 ±6.4	4.5±3.7	0.10
Negative cultures at one year	33 (60.0)	26(100)	7(21)	0.001
Outcome of patients				
Deaths at one year	9 (16.3)	0 (0.0)	9 (31.0)	0.001

Improved status at 1-year: Patients improved clinically and radiological and their microbiological samples were negative. **Unimproved status at 1-year:** The patients did not improve their clinical state or their radiological lesions or their microbiological samples did not negative.

ATS/IDSA: American Thoracic Society and the Infectious Disease Society of America

SD: standard deviation

S3 table. The general characteristics and treatment outcome of patients with positive HIV-serology.

Patients with positive HIV-serology	Total patients n=29 (%)	Patients with improved status n =17 (58.6%)	Patients with unimproved status n=12 (41.3%)	P value
Age (mean ± SD),years	49.2 ±-19.4	46.1±19.2	53.1±19.1	0.05
Sex				0.59
Male	22(75.8)	14 (82..3)	8 (66.6)	
Female	7(24.1)	3 (17.6)	4(33.3)	
Respiratory history				0.34
yes	6(20.6)	2(11.7)	4 (33.3)	
No	23(79.3)	15(88.2)	8 (66.6)	
Respiratory symptoms				
Cough	18(62.0)	11(64.7)	7 (58.3)	0.90
Sputum	9(31.0)	7(41.1)	2(16.6)	0.43
Radiology results				
Bronchiectasis	5(17.2)	2 (11.7)	3 (25.0)	0.63
Nodular opacities	9(31.0)	6 (35.2)	3(25.0)	0.25
Cavities	7(24.1)	1(5.8)	6(50.0)	0.08
Mycobacterial species				
M. avium complex (MAC)	17(58.6)	11(64.7)	6 (50.0)	0.76
M. simiae	4 (13.7)	2 (11.7)	2 (16.6)	0.99
M. fortuitum	3 (10.3)	2(11.7)	1 (8.3)	0.98
M. kansasii	2(6.8)	0(0.0)	2 (16.6)	0.19
ATS/ IDSA criteria	13(44.8)	8(47.0)	5(41.6)	0.99
ATS/IDSA microbiologic criteria	15 (51.7)	9 (52.9)	6 (50.0)	0.96
CD4<200	23 (79.3)	14(82.3)	9 (75.0)	0.98
Treatment (n, %)	16(55.1)	13(76.4)	3 (25.0)	0.04
Negative cultures at one year	17(58.2)	17(100)	0(0.0)	0.001
Outcome				
Deaths at one year	5 (17.2)	0 (0.0)	5(41.6)	0.04

Improved status at 1-year: Patients improved clinically and radiological and their microbiological samples were negative. **Unimproved status at 1-year:** The patients did not improve their clinical state or their radiological lesions or their microbiological samples did not negative.
ATS/IDSA: American Thoracic Society and the Infectious Disease Society of America

SD: standard deviation

S4 table. General characteristics and treatment outcomes analyzed by gender (Male/Female).

	Total patients n=119 (%)	Male Patients N=80 (67.2 %)	Female Patients N=39 (32.8%)	P value
Age (mean ± SD),years	50.4 ±-19.4	48.1 ±19.2	55.0±19.0	0.04
Respiratory history				
yes	70(58.8.)	44(55.0)	26 (66.6)	0.63
Respiratory disease				0.004
Cystic fibrosis	23(19.3)	16 (20)	7 (17.9)	
Bronchiectasis	23(19.3)	6 (7.5)	17 (43.5)	
Chronic obstructive pulmonary disease	18 (15.1)	16 (20)	2 (5.1)	
Respiratory symptoms				
Cough	79(66.4)	50(62.5)	29(74.3)	0.64
Sputum	61(51.3)	30(37.5)	31(79.4)	0.02
Radiology results				
Bronchiectasis	54(45.4)	29 (36.2)	25 (64.1)	0.04
Nodular opacities	24(20.1)	15 (18.7)	9(23.0)	0.45
Cavities	26(21.8)	20(25.0)	6(15.3)	0.05
Mycobacterial species				
M. avium complex (MAC)	55(46.2)	40 (50.0)	15 (38.4)	0.48
M. abscessus complex	17 (14.3)	10 (12.5)	7 (17.9)	0.58
M. fortuitum	16 (13.4)	10(12.5)	6(15.3)	0.77
M. simiae	11(9.2)	6(7.5)	5(12.8)	0.44
ATS/ IDSA criteria	68(57.1)	42(52.5)	26(66.6)	0.52
ATS/IDS microbiologic criteria	76(63.9)	50 (62.5)	26 (66.6)	0.87
Treatment (n, %)	63(52.9)	45(56.2)	18 (46.1)	0.61
Negative cultures at one year	61 (51.2)	44(55)	17(43.5)	0.61
Status				0.04
improved	46 (38.6)	36(45.0)	10 (25.6)	
unimproved	73 (61.3)	44 (55.0)	29 (74.3)	
Patient Outcome				
Deaths at one year	17 (14.2)	13 (16.2)	4(10.2)	0.58

Improved status at 1-year: Patients improved clinically and radiological and their microbiological samples were negative. **Unimproved status at 1-year:** The patients did not improve their clinical state or their radiological lesions or their microbiological samples did not negative.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1√	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	√	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2√	Explain the scientific background and rationale for the investigation being reported
Objectives	3√	State specific objectives, including any pre-specified hypotheses
Methods		
Study design	4√	Present key elements of study design early in the paper
Setting	5√	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6√	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7√	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*√	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9√	Describe any efforts to address potential sources of bias
Study size	10√	Explain how the study size was arrived at
Quantitative variables	11√	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12√	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*√	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*√	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (e.g., average and total amount)
Outcome data	15*√	Report numbers of outcome events or summary measures over time

Main results	16√	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17√	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18√	Summarise key results with reference to study objectives
Limitations	19√	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20√	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21√	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22√	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.