ORIGINAL ARTICLE

PULMONARY MYCOBACTERIOSIS: CLINICAL-EPIDEMIOLOGICAL PROFILE OF PATIENTS, TREATMENT MANAGEMENT, CLINICAL OUTCOME, AND ITS SPECIES IN THE STATE OF MATO GROSSO, BRAZIL (2013-2020)

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ABSTRACT

This study aimed to describe the clinical-epidemiological profile of patients in the State of Mato Grosso, who were affected by non-tuberculous mycobacteria (NTM), treatment management, clinical outcomes, and the species most commonly isolated from clinical samples. Between 2013 and 2020, the study analyzed 37 medical records from the Health Pulmonology sector of the Reference Center for Medium and High Complexity and it searched the Laboratory Environment Manager (GAL) system of the Central Public Health Laboratory of Mato Grosso. Patients with mycobacteriosis were predominantly diagnosed with MAC complex (*avium-intracellulare* complex) (n= 23.6%), with an average age of 62 years old; 51.4% were male, Caucasian (62%), and predominantly immunocompetent (HIV-negative). Most patients with comorbidities were older adults, they had sequelae of previous tuberculosis (56.8%), they were smokers (62.2%), and they had a low body mass index (29.7%) due to weight loss. Other patients had bronchiectasis (81.1%) and cavitary lesions (48.6%), with a lower incidence of chronic obstructive pulmonary disease (COPD). The municipalities with the highest rates of nontuberculous mycobacteria were Cuiabá (14 cases), Várzea Grande (five cases), Sinop (two cases), Nova Mutum (two cases), and Rondonópolis (two cases). This study presented data from the region, with a clinical, epidemiological profile, diversity of NTM species, and treatment management according to the patient's response to the specific treatment of the identified *Mycobacterium* and various outcomes.

KEY WORDS: Non-tuberculous mycobacteria; MAC complex *Mycobacterium*; comorbidities; tuberculosis; mycobacteriosis.

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INTRODUCTION

Non-tuberculous Mycobacteria (NTM) are *Mycobacterium tuberculosis*-like microorganisms that affect immunocompetent and immunocompromised patients. The introduction of molecular diagnostic methods has significantly facilitated the identification of mycobacterial species. However, little is known about these microorganisms' clinical and epidemiological profiles in Brazil. Most municipal laboratories in the State of Mato Grosso lack instruments to identify *Mycobacterium tuberculosis* and other NTM. This is a significant problem. In this study, we used the American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) protocol to examine populations affected by mycobacteriosis and determine the frequency of NTM (isolated species) in the State (Griffith et al., 2007). In addition to pulmonary NTM, they also cause hospital outbreaks (Fontana, 2008; Nunes et al., 2014), which occur here and they are called atypical mycobacteria (caused by *M. abscessus* and *M. fortuitum*). The medications used in the clinical management of NTM and the duration of treatment in each group were investigated. The study also evaluated the distinct species and increasing diversity among mycobacteria, including similarities in associated chronic respiratory symptoms such as persistent cough, weight loss, and loss of appetite present in most patients aged > 60 years old, and further evaluated the comorbidities which influences the mortality rate.

MATERIAL AND METHODS

Study Group and Ethical Aspects

Patient data were obtained from the medical records of the Tuberculosis Reference Center of the Medium and High Complexity Reference Center (CERMAC/ SES/ MT), which provides services for all patients in the State of Mato Grosso. Registered patients were examined using the Unified Health System (SUS). The Research Ethics Committee of Mato Grosso School of Public Health approved the study and provided a Certificate of Submission for Ethical Review (CAAE no. 43125721.4.0000.5164).

Samples processing

The samples used in this study were obtained from the Central Health Laboratory from the State of Mato Grosso between 2013 and 2020. Mycobacterial cultures were analyzed using the BD BACTEC™ 320 automated method (Becton, Dickinson & Company, Sparks, MD, USA). Samples (sputum or bronchoalveolar lavage) were decontaminated using the modified Petroff Method and they were cultured in Lowenstein Jensen (LJ) medium (DIFCO),

enabling the identification of NTM cultures (positive in at least two samples characterizing infection and persistence, except samples from sterile sites). Colonies grown on Lowenstein-Jensen (LJ), LJ-TCH (Thiophene-2-carboxylic acid hydrazide), and LJ-PNB (paranitrobenzoic acid) media were identified based on growth patterns and phenotypic characteristics. The isolates showed characteristic positive acid-alcohol resistance (BAAR positive), a negative string effect, and negative results for the MPT64 antigen (immunochromatographic) (Allere). Based on these results, the isolates were confirmed as NTM (Non-tuberculous *Mycobacterium*). All isolates followed the American Thoracic Society (ATS) protocol (Griffith et al., 2007), with a positive result for acid-alcohol resistance and cultures with growth of identical NTM species (at least two positive or paired samples). *Mycobacterium* species were further identified using molecular biology techniques (PRA-hsp65 restriction enzyme, probe identification, and sequencing) performed at the National Reference Laboratory (Centro de Referência Professor Hélio Fraga - RJ). Drugs used in the management of mycobacteria were studied using the minimum inhibitory concentration (MIC) method (Ministry of Health, 2021).

Statistical analysis

Categorical variables were summarized by absolute (n) and relative (%) frequencies, and continuous variables by means and 95% confidence intervals (95% CI) or medians and interquartile intervals (IQR), depending on the type of distribution assessed by the Shapiro-Wilk test. Association between categorical variables was performed using Pearson's chi-square test or, when necessary, by Fisher's exact test. A multivariate model was adjusted using binary logistic regression to eliminate potential confounding bias and to identify independent factors associated with death. Statistical significance was considered at $p < 0.05$, in the two-tailed test, and all analyses were performed using R software version 4.2.1 through its integrated development environment RStudio 2022.07.1. (Copyright© 1989, 1991 Free Software Foundation, Inc., 51 Franklin St, Fifth Floor, Boston, MA, 02110-1301 USA).

RESULTS

The study presented data from the medical records of reference care (Sanitary Pulmonology/ CERMAC) of 37 patients affected by mycobacteriosis between 2013 and 2020, with characteristics such as age, gender, race, residential area, occupation, and geographical distribution according to the municipalities of residence (Table 1). Patients with mycobacteriosis were aged 56 to 75 years old, with an average age of 62; 51.4% were white men and they lived in urban areas.

Table 1. Clinical, regional and occupational characteristics of patients with NTM (Non-Tuberculous Mycobacteria).

	Number of cases	%
Age (years)		
30 - 55	11	29.7
56 - 75	21	56.8
76 - 80	5	13.5
Gender		
Male	19	51.4
Female	18	48.6
Race		
White	23	62.2
Brown	14	37.8
Residencial area		
Urban	29	78.4
Rural	8	21.6
Occupation		
Gold River mining company	2	5.4
Driver	3	8.1
Teacher	3	8.1
Nursing technician	3	8.1
Housewife	4	10.8
Field activities	9	24.3
Others	13	35.2
Mato Grosso Region		
Meso North	7	19.4
Meso South-center	21	58.3
Meso Southeast (L)[*]	4	11.1
Meso South-west (O)[*]	2	5.6
Meso North West	2	5.6
Federative Unit (State)		
Mato Grosso	37	97.3
Others	1	2.7
Weight		
Initial weight (kg)	60	(51.0, 66)
Final weight (kg)	50	(44.0, 60)

Smoker		
Yes	23	62.2
No	14	37.8
Alcoholic		
Yes	8	21.6
No	29	78.4
BMI < 18.5#		
Yes	11	29.7
No	26	70.3

*L: East; O: West; #BMI: Body Mass Index.

They presented sequelae of previous tuberculosis (56.8%), mainly they were smokers (62.2%) and non-drinkers (78.4%), and they had lower body mass index (BMI) (Table 1). 57% of the patients were presented with relevant body weight loss, asthenia, and inappetence. Most patients had bronchiectasis (81.1%) and cavitary lesions (48.6%); however, these diseases were less frequent in individuals with Chronic Obstructive Pulmonary Disease (COPD) (32.4%) (Table 2).

NTM are dispersed in all types of water, soil, fish, and stone. Therefore, data related to aspects of professional activities and types of residences were observed. Most of them lived in urban areas; however, 37% were involved in soil- and dust-related activities, such as excavation and driving. Alcoholism, smoking, and the significant diseases observed in these patients have been also registered.

Patients with mycobacteriosis were white, with an average age of 62, mostly male, and HIV-negative. They presented sequelae of previous tuberculosis (56.8%), they were primarily smokers (62.2%) and non-drinkers (78.4%), and they had reduced body mass index (BMI) (Table 1). Of these patients, 57% presented with relevant body weight loss, asthenia, and inappetence. Most patients had bronchiectasis (81.1%) and cavitary lesions (48.6%); however, these were less frequent in individuals with COPD (32.4%) (Table 2). Most patients had bronchiectasis (81.08%) and cavitary lesions (48.6%); however, these were less frequent in individuals with COPD (32.4%) (Table 2). Sputum was the most obtained sample type (92%). Most of them live in the Meso-central southern region of Mato Grosso, where the capital Cuiabá is located, with 3.6 million inhabitants (IBGE, 2022). As they are respiratory symptomatic, the sample collected was sputum (92%).

Table 2. Comorbidities, relapses and imaging of patients with pulmonary Mycobacteriosis

Variables	Number of cases (%)
HIV	
No	33 (89.2)
Yes	4 (10.8)
Tuberculosis sequelae	
No	16 (43.2)
Yes	21 (56.8)
Diabetes	
No	32 (86.5)
Yes	5 (13.5)
Systemical arterial hypertension	
No	33 (89.2)
Yes	4 (10.8)
Hepatitis B	
N/A	1 (2.7)
No	36 (97.3)
Bronchiectasis	
No	7 (18.9)
Yes	30 (81.1)
COPD*	
No	25 (67.6)
Yes	12 (32.4)
Outcomes	
Cure	16 (43.2)
Death	12 (32.4)
Abandonment	2 (5.4)
In progress	5 (13.5)
Transference	2 (5.4)
Images	
Granulomatous process	2 (5.4)
Fibroatelectasis	3 (8.1)
Centrilobular emphysema	3 (8.1)
Residual injuries	2 (5.4)
Diffuse nodules	4 (10.8)
Tree in bud	5 (13.5)
Cavity lesions	18 (48.6)

*COPD: Chronic Obstructive Pulmonary Disease

A study of the images of patients affected by mycobacteriosis revealed cavitary lesions (48.6%), diffuse nodules (10.8%), tree-in-bud lesions (13.5%), and fibroatelectasis (8.1%), which are often observed in both lungs (Table 2). Patients who experienced long-term adverse effects (32%), as epigastric malaise, nausea, headache, and joint pain, also abandoned treatment. This applies to patients affected by mycobacteriosis, who experience considerable discomfort due to the toxicity and the adverse effects caused by the lengthy treatment period.

Table 3 presents the different isolates of mycobacteria obtained from clinical samples of these patients, number (n) and frequency (%). Isolates of samples from the same patients were collected at Lacen-MT, and different NTM species were obtained through bacteriological examinations. 62.2% of isolated nontuberculous mycobacteria belonged to the MAC complex (*M. avium, M. intracellulare, M. massiliense,* and *M. columbiense*). Other mycobacterial NTM species of clinical relevance were mycobacteria belonging to the *M. abscessus* (15.5%), also called MCR (Fast Growing Mycobacteria) as well as *M. fortuitum* and *M. asiaticum*, both 5.4% (Table 4).

Table 3. Multivariate analysis of risk factors

Variables	OR[*]	95% CI[#]	p-value
Elderly			
No	-	-	-
Yes	12.3	1.51, 308	0.047[+]
Weight loss [++]			
Low weight-loss	-	-	-
High weight-loss	0.93	0.16, 5.16	0.938
Time until result			
Precocious	-	-	-
Late	0.20	0.02, 1.41	0.117
Smoking			
No	-	-	-
Yes	0.58	0.07, 4.53	0.600
COPD[&]			
No	-	-	-
Yes	0.97	0.13, 6.64	0.975

[*]OR: Odds-ratio; [#]CI: Confidence Interval; [&]COPD: Chronic Obstructive Pulmonary Disease[+] p< 0.05 statistical significance; [++] during treatment.

Table 4. Microorganisms and isolated species.

Microorganisms	n	(%)
Total Complexo MAC	23	(62.2)
Mycobacterium avium	7	18.9
M. avium/ intracellulare	3	8.1
M. intracellulare	5	13.5
M. intracellulare/ M. chimaera	7	19.0
M. colombiense	1	2.7
M. abscessus complex	5	(13.5)
M. abscessus	2	5.4
M. abcessus subesp bolletii	3	8.1
Others *Mycobacterium*	9	(24.3)
M. asiaticum	2	5.4
M. fortuitum	2	5.4
M. interjectum	1	2.7
M. kansasii	1	2.7
M. terrae	1	2.7
M. sherrisii	1	2.7
M. simiae	1	2.7

Most reside in the meso-central-south region of Mato Grosso, where the metropolitan capital of Cuiabá is located, with 3.6 million inhabitants (IBGE, 2022). The municipalities with the highest rates of NTM infection were Cuiabá (14 cases), Várzea Grande (five cases), Sinop (two cases), Nova Mutum (two cases), and Rondonópolis (two cases).

Table 5 shows the different treatment regimens used for these patients. However, management should follow the Ministry of Health guidelines (Brazil, 2021), which details the doses and drugs according to the isolated species. Observing the treatment duration and challenges arising from the resistance of microorganisms to drugs and their toxicity is important.

Figure shows the distribution of outcomes in which a cure was observed in most patients (14 cases). However, there were significant number of deaths (n= 12) and abandonment of treatment (n= 6).

Table 5. Treatment regimens for patients of the Reference Center for Sanitary Pneumology (2013-2020).

Group	Group 1	Group 2	Group 3	Group 4
Number of Patients	13	04	03	03
Clarithro-Ethambutol-Rifamicin	Clarithromicin Ethambutol + Rifampicin ou Rifabutin	Clarithromicin Ethambutol + Levofloxacin	Clarithromicin Ethambutol + Amikacin	Clarithromicin + Amikacin + Quinolon (Morfloxacin/ Norfloxacin)

Four Groups: Individual schemes used to treat NMT, management guided by the Ministry of Health.
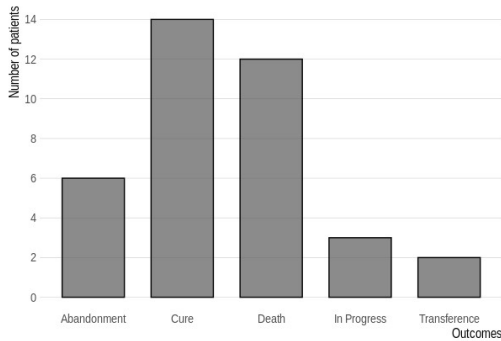
Figure. Distribution of Non-Tuberculous Mycobacteria cases according to outcome.

DISCUSSION

Studies of Mycobacteriosis caused by NTM are more recent than tuberculosis and they are a major cause of chronic respiratory diseases. They must first be distinguished from the so-called "colonizing mycobacteria" present in the respiratory tract, following protocols (Griffith et al., 2007) that aid in the endeavor. Because they are dispersed in the environment, approximately 70% of the isolated NTM colonize mycobacteria from the respiratory tract. Most confirmed cases (97%) were caused by pulmonary mycobacteriosis. This was determined by the ATS protocols from sputum samples and patients residing in the State of Mato Grosso, except the ones from the State of Amapá.

The investigation of pulmonary mycobacteriosis begins with the suspicion of tuberculosis; however, although they are all mycobacteria, they are quite distinct from *M. tuberculosis* (tuberculosis). The incidence of NTM is increasing in several countries (Zweijpfenning et al., 2018), including Brazil. Approximately 200 species of NTM cause mycobacteriosis with clinical relevance (Fedrizzi et al., 2017), and despite the similarity in symptoms, they are distinct in their *in vitro* growth and phenotypic characteristics. Although sputum is the most frequently collected sample, it is not always feasible. In such instances, bronchoscopy is suggested to obtain an alveolar bronchial lavage and biopsy for cytopathological studies to identify cells with granulomatous inflammation (Griffith et al., 2007). Part of the dry cough group of patients may use the procedure (bronchoscopy) when possible, because mycobacteriosis disease is characterized by alternating productive cough/ dry cough periods.

In this study, 89% of patients were immunocompetent, with only 11% being immunocompromised (HIV-positive); these characteristics were also found in the State of Rio de Janeiro (De Mello et al., 2013), as were the mycobacterial species, *M. kansassii*, MAC complex, and *M. abscessus* in descending order of prevalence. Carneiro et al. (2018) and Costa Silva et al. (2018) recorded the presence of the MAC complex at approximately 35% - 40% in the city of Porto Alegre and in the State of Minas Gerais; however, Ueki et al. (2005) observed a similar percentage in the State of São Paulo (64.9). These mycobacteriosis were also present in 56.8% of previously treated patients with tuberculosis with cavitary sequelae (Image), according to the multivariable analysis of the 37 affected patients. Other pathologies include diabetes mellitus, hepatitis B, systemic arterial hypertension, bronchiectasis, and COPD.

MAC complex (62.2%), *M. abscessus* (13.5%), *M. asiaticum* (5.4%), and *M. fortuitum* (5.4%) were the mycobacteria most frequently isolated from the patients affected by the disease. Bacteriological examination of mycobacteria (with high sensitivity and specificity) differentiates NTM from *M. tuberculosis*, thus distinguishing mycobacteriosis from tuberculosis. This is the only test that allows detailed studies to identify NTM species and to perform the minimum inhibitory concentration (MIC) drug sensitivity tests.

For the disease's end process, we observed a complex, lengthy, and prolonged treatment, with a microbiological cure after 12 months, without NTM growth, in only 43% of the treated patients. This study's mortality rate was 27%, similar to the current rate in the city of Fortaleza, Ceará (24.6%) (De Lima Mota et al., 2020). Studies in North America and Europe also corroborate the findings of this study with the presence of microorganisms belonging to the MAC complex (*M. intracellulare, M. avium, M. masseliense*, and *M. colombiense*), with mortality rates ranging from 33% to 35% (Zweijpfenning et al., 2018).

Bacteriological examinations may distinguish *M. tuberculosis* from other types of NTM. In the Lowenstein-Jensen medium, mycobacteriosis, and tuberculosis are caused by mycobacteria isolated from suspected clinical specimens by specific cultures. Generally, colonies exhibit rapid growth and they are not pigmented, except for longer incubation periods, during which MAC complex colonies exhibit a slight yellowish pigmentation.

Ito et al. (2020) observed statistically significant macrolide resistance in HIV-negative patients receiving dual therapy (clarithromycin-ethambutol) or triple therapy (clarithromycin-ethambutol-rifampicin). Triple therapy was the most effective in reducing bacteremia in AIDS patients with pulmonary mycobacteriosis, according to Adachi et al. (2020).

The efficacy of this treatment regimen was demonstrated in a retrospective series in which negative cultures were maintained in 82% of patients; however, a 48% relapse rate was observed (Wallace et al., 2014). Despite the limited number of patients with mycobacteriosis in this study, triple-type treatment was observed in 62% (groups 1, 2, 3, and 4) with a similar relapse rate of 37.8%. The resistance of the two most frequent species of the MAC complex (*M. intracellulare* and *M. avium*) has been extensively investigated (Wang et al., 2021). Antimicrobial resistance was more prevalent in *M. intracellulare* than in *M. avium* (except for clarithromycin, ethambutol, and ciprofloxacin), which may explain the higher number of deaths associated with *M. intracellulare* (six cases) in this study (Mato Grosso), compared with *M. avium* (one death). Boorgula et al. (2021) examined two types of drugs, rifabutin, and rifampicin, and observed that rifabutin reached higher serum levels in HIV-positive patients than rifampicin. Only one case of adverse effects of rifabutin was reported in this study (Figure).

From 2013 to 2020, Mato Grosso had 37 cases of mycobacteriosis, a population of 3.6×10^6 inhabitants (IBGE census 2022), with a prevalence of 1.6 cases $\times 10^6$ inhabitants per year, which was confirmed in the National Reference Laboratory (CRPHF-RJ) by identification and MIC test, performed according to the species obtained. A limitation of the present study is the small number of NTM cases; however, it provided essential data on the clinical and epidemiological profile and treatment of NTM. The current research from Mato Grosso significantly contributes to data on the prevalence and distribution of NTM species isolated in Brazil (Ueki et al., 2005; Pedro et al., 2017; Carneiro et al., 2018).

Mycobacteriosis is prevalent in the municipalities of Cuiabá and Várzea Grande, which are hubs of high population density in Mato Grosso, according to the most recent census (IBGE, 2022).

Due to the similarities between tuberculosis and mycobacteriosis, lungs X-ray and computerized tomography examinations of images suggested necessary pulmonary alterations, which were infectious, but were insufficient to distinguish between the two diseases. Therefore, specific bacteriological

tests revealed other mycobacteria (NTM), and treatment and monitoring with monthly sputum cultures for mycobacteria began only after the species was identified.

Additionally, researchers have studied double- and triple-treatment schemes. After analyzing all treatments administered in this group and identifying the most frequent species of NTM, a study was conducted on treatments in which the drugs were grouped and divided into four groups. We followed the detailed guidelines of a recently published manual on NTM (Brasil, 2021). In this study, we grouped the possibilities of choice depending on the mycobacterial species isolated, with a differential drug located in the third drug of each group. Group 1, C (clarithromycin), E (ethambutol), and Rifampicin or Rifabutin (rifamycin group); Group 2, C, E, and Levofloxacin; Group 3, C, E, and Amikacin, and Group 4, C and E, and quinolones. Each category was selected based on the characteristics of each drug.

Treatment success depends on the sensitivity of the microorganism to the drugs, beneficial patient/ time interactions, and pharmacokinetics/ adverse effects on the patient during this period. Mycobacteriosis is chronic, and its treatment time is often prolonged (Dartois & Dick, 2022); its completion is directly associated with immune status, drug interaction with the causative microbial agent, and patient medication adherence. Careful identification and treatment of mycobacteria, progress monitoring during treatment, and prevention of drug interactions that can occur during combination therapy are required for treatment. During the treatment, only 16% of patients in this study experienced adverse effects such as optic neuritis and visual changes from ethambutol, ototoxicity (tinnitus, hearing loss) from amikacin, anaphylactic reactions from rifampin, rifabutin, ethambutol, arthralgias from levofloxacin, dizziness, nausea, and epigastralgia. Murcia et al. (2006) & Kim et al. (2013) demonstrated the hepatotoxicity of rifampicin and visual disturbances caused by ethambutol, respectively.

Most patients are cured; however, a mortality rate of 32% has been reported. The analysis of mycobacteriosis in the period shows a high number of deaths (12 cases) and an expressive number of abandonments of the treatment (six cases). Thus, there were 4.6 cases of mycobacteriosis treated/ per year and 1.75 cases of relapse per year. Considering the population of Mato Grosso (IBGE, 2022), the prevalence coefficient (Mato Grosso-MT State) is 1.6×10^6 inhabitants/ year of mycobacteriosis cases (MNT). Previous studies on the quality of life associated with the MNT have identified difficulties in routine tasks, social isolation, mental health problems, fatigue, and tiredness. These findings reinforce that pulmonary mycobacteriosis has a great impact on quality of life (Fedrizzi et al., 2017) because due to old age, they also present other diseases and generally use other medications.

NTMs represent a significant challenge both in Brazil and worldwide. Multidisciplinary teams composed of physicians, pharmacists, microbiologists, and nurses must focus on alleviating symptoms and treating NTMs less aggressively, thereby increasing treatment adherence, especially on older people. A better treatment compliance must be ensured (Kumar et al., 2022), and the adverse treatment reactions need to be overcome, with better overall outcomes, especially for older patients.

In conclusion, this study presents data from the region with a clinical, epidemiological profile, diversity of NTM species, and the treatment management according to the patient's response to the specific treatment of the identified *Mycobacterium* and various outcomes. The prevalence of mycobacteriosis in Mato Grosso was 1.6 cases $\times\ 10^6$ inhabitants/ year. The MAC complex and *M. abscessus* are the most frequent NTM responsible for most pulmonary NTM cases.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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