

Therapeutic Management Strategies Among Immunocompetent Infants with Nontuberculous Mycobacterial Pulmonary Infection

Alice Bai¹, Hari Dandapani², Amrita Dosanjh³

¹The Pritzker School of Medicine, University of Chicago, Chicago, IL, USA; ²The Warren Alpert Medical School, Brown University, Providence, RI, USA; ³Department of Pediatrics, RCHSD/Pediatric Respiratory, San Diego, CA, USA

Correspondence: Amrita Dosanjh, Department of Pediatrics, RCHSD/Pediatric Respiratory, San Diego, CA, 92123, USA, Tel +1-858-966-5846, Email pulmdl@gmail.com

Purpose: The prevalence of pulmonary nontuberculous mycobacteria (NTM) infection and disease is increasing globally. Pediatric studies on treatment of pulmonary NTM disease in immunocompetent infants are limited, and adult guidelines lack details regarding age-specific management strategies. This systematic review analyzes pharmaceutical, procedural, and supportive management strategies for pulmonary NTM infections in immunocompetent infants based on published case reports and series.

Methods: A systematic review of PubMed for case reports on pulmonary NTM infections in immunocompetent infants (≤ 24 months) until December 2023 was conducted. Demographic information, therapeutic interventions, procedural details, and patient outcomes were extracted to Covidence. Data on therapeutic strategies were summarized descriptively.

Results: Twenty-six case reports describing 33 infants with pulmonary NTM were identified. Study demographics included: 55% female, median age at diagnosis was 12 months, and *Mycobacterium avium* complex (58%) was the most common NTM strain. Most patients (94%) received antibiotic therapy, with a median treatment duration of 30 weeks. Common regimens included combined ethambutol with rifampin ($n=9$) or clarithromycin ($n=6$), and clarithromycin with amikacin ($n=6$). Most patients started on therapy for tuberculosis before switching treatment courses after NTM diagnosis. Common antibiotic classes after NTM diagnosis were macrolides, antituberculous, and aminoglycosides. Non-pharmaceutical therapies included 79% undergoing diagnostic bronchoscopy, 39% receiving tissue debulking, 33% undergoing surgical biopsy for diagnostic confirmation, and 12% requiring lung resection. Two patients underwent surgical interventions without antibiotics. Supportive therapies included non-invasive supplemental oxygen (12%) and mechanical ventilation (6%), with three patients admitted to intensive care units. Overall survival rate was 94%.

Conclusion: This study reports diverse therapeutic approaches to management of immunocompetent infants with diagnosed pulmonary NTM disease, which utilized varying antibiotics and procedural interventions. Although few patient deaths were reported, these results suggest a need for additional prospective studies to compare efficacy of treatment regimens and establish tailored pediatric guidelines for disease management.

Keywords: pulmonary NTM, antibiotic therapy, infant infection, *M. avium* complex

Introduction

Nontuberculous mycobacteria (NTM) are a group of opportunistic bacteria that manifest as lymphadenitis or pulmonary, cutaneous, or disseminated infection.¹ Although pulmonary NTM infections are generally associated with chronic disease, including cystic fibrosis and immunodeficiency,² epidemiologic data show that rates of pulmonary NTM infections are increasing in the general population.^{3–6} Limited studies have reported increases in NTM infection amongst children as well.^{7,8}

NTM pulmonary infection is uncommon amongst children in comparison to lymphadenitis.⁹ Pulmonary NTM disease is typically associated with cystic fibrosis-related bronchiectasis or immunodeficiency,⁷ and management of patients with these underlying diseases may include transplantation and other strategies intended to target multiple systems that may

not be appropriate in immunocompetent patients. Conversely, some treatments for pulmonary NTM may be less effective in patients with pre-existing structural and immunologic deficits.^{10,11} As a result, the paucity of data regarding the management of pulmonary NTM disease among otherwise healthy infants who develop this infection represents a distinct knowledge gap.

Recommendations for diagnosis and management are generally based on guidelines established for adult patients,¹² such as for susceptibility testing, antibiotic therapy, and surgical management. Applying these guidelines to pediatric populations is imperfect, as pediatric patients may be subject to differing response to pulmonary therapies and age-specific pharmacokinetics and dynamics such as lower levels of plasma binding proteins or maturational changes in hepatic and renal metabolism of compounds, as well as distinct side effect profiles such as unique adverse drug reactions to tetracyclines reported solely in children under the age of 8.^{13,14} For example, calculations to adjust dosing intervals or dosage of renally cleared drugs are complicated by challenges in accurately assessing GFR or tubular secretion in young infants.¹⁵ Studies exploring the pathogenesis of pulmonary NTM infections in adults have suggested that phenotypic characteristics such as shortened anterior-posterior thoracic dimension, as well as immunologic differences in IFN- γ , IL-12, and TNF- α levels may play a contributory role in pulmonary NTM pathogenesis.¹⁶ However, the implications of these factors on the pathogenesis of pulmonary NTM in infants are unclear and must be considered in the context of immune development and differing response in infants compared to adults, such as delayed IL-12 synthetic capacity that extends into late childhood.^{17,18}

This project aims to address the absence of aggregated data in the literature focused specifically on the treatment and management of pulmonary NTM infections in otherwise healthy infants, including procedural, pharmaceutical, and supportive management techniques.

Materials and Methods

Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,¹⁹ we conducted a literature search of PubMed for all articles published up to December 2023. Our search focused on identifying studies addressing NTM pulmonary infections specifically in otherwise healthy infants. Search terms included “infant” “NTM” “pulmonary” “Mycobacterium abscessus” and “Mycobacterium Infections, Nontuberculous.” We utilized Medical Subject Headings (MeSH) terms in PubMed to refine our search and applied specific exclusion criteria to avoid irrelevant results.

Specifically, the search was conducted through four specific PubMed queries with filters for Case Reports, Humans, English, and Infant (birth-23 months): 1. ((infant) AND (NTM)) AND (pulmonary); 2. ((Mycobacterium abscessus) AND (infant)) AND (pulmonary); 3. (Mycobacterium abscessus) AND (infant); 4. (“Mycobacterium Infections, Nontuberculous”[Mesh]) NOT (cystic fibrosis).

Eligibility Criteria

Our search criteria included all English-language case reports documenting treatment for NTM pulmonary infection in infants, defined per American Academy of Pediatrics guidelines²⁰ as ≤ 24 months and/or under, at the time of symptom presentation.

We excluded non-English studies and those that presented only aggregate data and thus lacked therapeutic data for individual patients. Cases were also excluded if they lacked clear documentation of NTM diagnosis with documented pulmonary symptoms or if they were reported in languages other than English. Pulmonary NTM infections in included cases were diagnosed according to the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines, or according to the case report authors’ reasoning from clinical and microbiologic findings when ATS/IDSA guidelines were not directly referenced. Given the predisposition for opportunistic infection associated with cystic fibrosis and immunodeficiency conditions, we excluded cases diagnosed with these conditions. This search strategy is adapted from our previous work, but it has been updated to include more recent works and refined to exclude any documented cases of immunodeficiency.²¹

Data Extraction

Data extraction was conducted using Covidence, an online platform designed for systematic review management. Two reviewers (AB and HD) independently screened abstracts of the case reports for potential inclusion. In cases of disagreement between the two reviewers, a consensus was reached through discussion. Following the abstract review, the full texts of selected studies were assessed by the two reviews to ensure that they met the eligibility criteria. Studies meeting all criteria were included for data extraction, and any studies failing to meet these criteria were excluded from further analysis.

Extracted data were categorized under standardized fields that included demographic information, therapeutic interventions, additional procedural details, and patient outcomes. Specifically, data fields included patient gender, age at diagnosis, identified NTM strain, course and duration of pharmacotherapy, immune status, any additional treatment procedures undertaken, and outcomes recorded at the time of the case report's publication. Information not presented in the case report was assumed to be noncontributory.

To standardize data, we converted patient age in days to months, considering each month as four weeks. Similarly, treatment durations reported in months were converted to weeks. Any reports mentioning "antituberculous therapy" without specifying the drug regimen were assumed to utilize empiric four-drug tuberculosis therapy of isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE) unless otherwise specified.

Statistical Analysis

Descriptive statistics were used to analyze and summarize the extracted data. Data from each included case were extracted from Covidence. Quantitative variables were analyzed based on their frequency, mean, and standard deviation, while qualitative variables were analyzed based on their proportions or percentages. Data points extracted for quantitative analysis included patient demographics, NTM strain, drug regimen, duration of treatment and hospitalization, as well as patient immune status. Additionally, procedural interventions and patient outcomes were analyzed quantitatively.

Outcomes were recorded at the time of each respective case report's publication, and pooled data were used to calculate descriptive statistics such as sums, percentages, means, and medians ($\pm$ IQR) where applicable. In cases where no data were reported for a given field, we assumed the absence of any significant findings relevant to that specific data point. These assumptions were incorporated into our data analysis to ensure that findings accurately reflected the limitations and available information within the reviewed case reports.

Results

Search Results

The initial PubMed search yielded a total of 283 articles across four queries. After removing 48 duplicates, 235 articles remained for further screening. The title and abstract screening excluded 108 studies that did not meet the eligibility criteria. The remaining 127 studies proceeded to full-text evaluation, during which 101 additional studies were excluded due to lack of relevance, insufficient data on NTM pulmonary infection in infants, or otherwise not meeting the inclusion criteria. This process ultimately yielded a final sample of 26 published case reports,^{22–47} comprising a total of 33 patients, as several reports included multiple infants concurrently hospitalized with confirmed pulmonary NTM infection (Figure 1).

Patient Characteristics

Of the 33 patients documented in the case studies, 36% (n=12) were male, 55% (n=18) were female, and 9% (n=3) did not specify patient sex. Median age was 12 months (IQR: 5–19 months) at the time of diagnosis. Among the identified NTM strains, 58% (n=19) were *Mycobacterium avium* complex (MAC), 18% (n=6) were *Mycobacterium abscessus*, 12% (n=4) were *Mycobacterium fortuitum*, and 6% (n=2) were *Mycobacterium chelonae*. *M. smegmatis* was cultured in 1 patient, and 1 patient had an unidentified NTM strain. Median length of hospitalization was 25 days (IQR 14–112). Of the 33 patients included in the study 94% (n=31), were reported as alive at the time of the publication of the case report, while 6% (n=2) were reported as deceased.

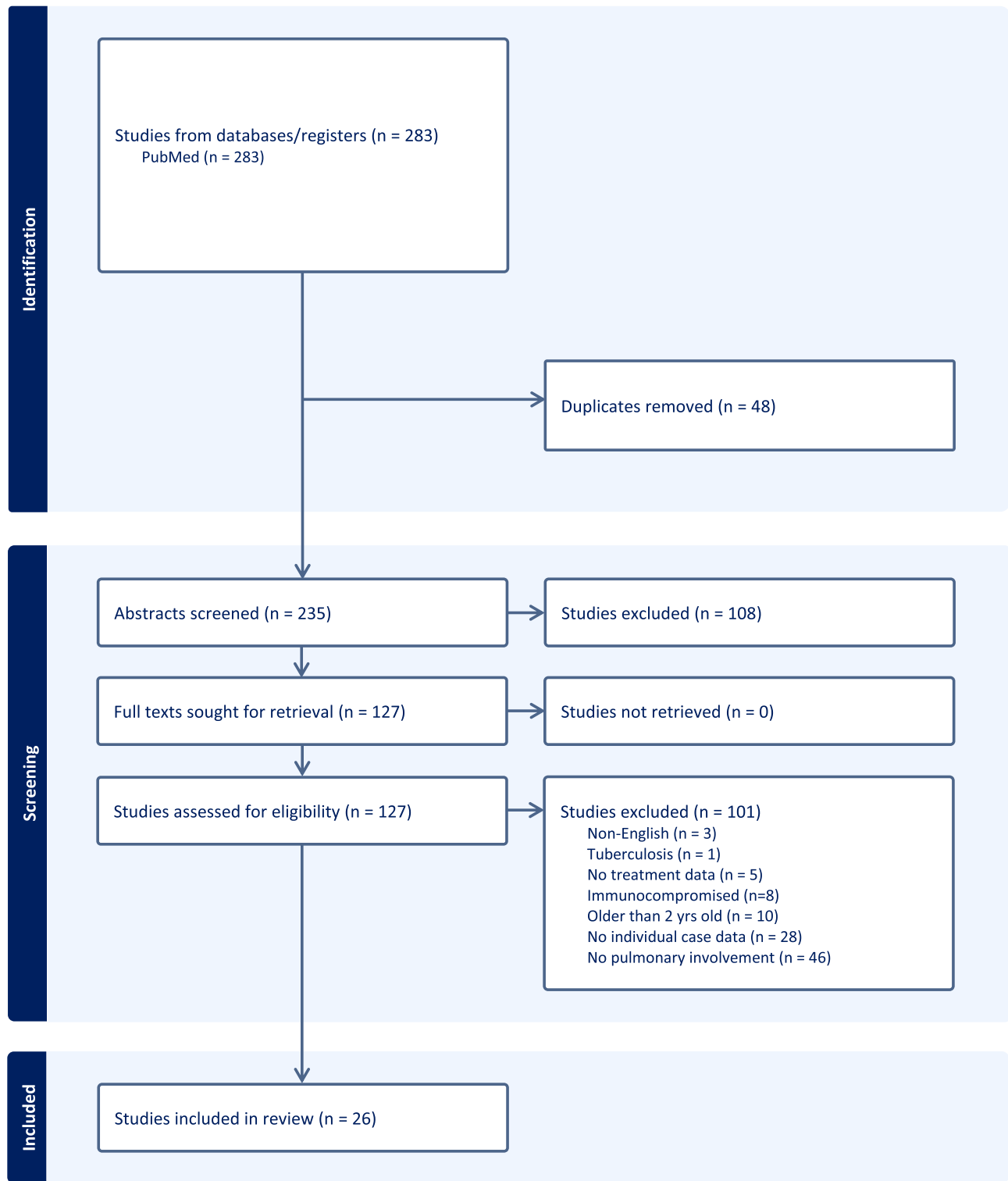


Figure 1 PRISMA Flow Diagram of Search Process.

Pharmaceutical Therapeutics

Antibiotic treatment duration varied from 0 to 432 weeks, with a median duration of 30 weeks (IQR=10–55).

Patients in the study received multiple medications to manage NTM infections. Overall, 94% (n=31) of patients were treated with antibiotic therapy. Two patients did not receive antibiotic therapy. Both of these patients underwent either surgical resection or subtotal excision of the bronchial mass as their primary treatment.

Pre-Admission Pharmacotherapies

Therapeutic strategies initiated before patients were admitted for further treatment were reported in 17 cases. Patients received bronchodilators in 6 cases and corticosteroids in 3 cases. Nine cases referenced antibiotic therapy, which included 2 cases of azithromycin, 2 cases of amoxicillin, 2 cases of ceftriaxone, 1 case of cefdinir, 1 case of clindamycin, 1 case of roxithromycin, and 1 case of trimethoprim-sulfamethoxazole (TMP/SMX).

Post-Admission, Pre-NTM Diagnosis Pharmacotherapies

Of the total 33 patients, 21 cases reported pharmacotherapeutic management after admission, but before a diagnosis of NTM was made. This included 18 cases where anti-tuberculosis medication was started, with 18 patients receiving rifampin, 18 patients receiving isoniazid, 17 patients receiving pyrazinamide, and 8 patients receiving ethambutol. Medication treatment before NTM diagnosis is summarized in [Table 1](#).

Post-NTM Diagnosis Pharmacotherapies

The medications that patients received after NTM were identified as the causative agent for pulmonary infection are detailed in [Table 2](#). Unique classes of antibiotics used in patient management are detailed in [Table 3](#). Changes in pharmacotherapeutic management were described among 17 patients after NTM was diagnosed as causative of patients' pulmonary infections. The median number of antibiotics given after definitive NTM diagnosis was 3 (IQR: 2–4).

Patients were often treated concurrently with multiple antibiotics. Macrolides (n=23) were commonly paired with quinolones in 9 cases, rifampin in 8 cases, ethambutol in 8 cases, aminoglycosides in 7 cases, and cephalosporins in 5

Table 1 Most Frequently Administered Medications Before Non-Tuberculous Mycobacterial Diagnosis

Medication	Number of Patients Receiving
Isoniazid	18
Rifampin	18
Pyrazinamide	17
Ethambutol	8
Corticosteroids	5
Ceftriaxone	3
Gentamicin	2
Vancomycin	2
Ampicillin	2
Azithromycin	2
Clindamycin	2
Streptomycin	1
Amoxicillin + Clavulanic acid	1
Piperacillin + Tazobactam	1
Cefdinir	1

Table 2 Most Frequently Administered Medications After Non-Tuberculous Mycobacterial Diagnosis

Medication	Number of Patients Receiving
Clarithromycin	17
Rifampin	13
Amikacin	11
Ethambutol	10
Azithromycin	7
Ciprofloxacin	6
Isoniazid	5
Imipenem	4
Corticosteroids	4
Cefoxitin	4
Rifabutin	4
Meropenem	2
Clofazimine	2
Trimethoprim-Sulfamethoxazole	2
Cilastatin	1
Levofloxacin	1
Cephalexin	1
Streptomycin	1
Para-aminosalicylic acid	1
Ethionamide	1
Linezolid	1
Moxifloxacin	1
Cefprozil	1
Tigecycline	1
Ofloxacin	1

Table 3 Antibiotic Classes Used to Treat >1 Patient After Non-Tuberculous Mycobacterial Diagnosis

Medication Class	Number of Patients Receiving
Aminoglycosides	11
Macrolides	23
Carbapenems	5

(Continued)

Table 3 (Continued).

Medication Class	Number of Patients Receiving
Cephalosporins	5
Quinolones	9
Sulfonamides	2
Antituberculosis (any HRZE)	14
Isoniazid	5
Rifampin	13
Pyrazinamide	3
Ethambutol	10

cases. Aminoglycosides (n=11) were commonly paired with cephalosporins in 6 cases, carbapenems in 4 cases, quinolones in 4 cases, rifampin in 3 cases, and ethambutol in 3 cases.

For specific medications, the most common pairings (n≥5) were ethambutol with rifampin (n=9) or clarithromycin (n=6), clarithromycin with amikacin (n=6) or rifampin (n=5), and rifampin with isoniazid (n=5).

Notable three-medication regimens were ethambutol, rifampin, and a macrolide in 7 cases; a macrolide, quinolone, and aminoglycoside in 4 cases; a macrolide, cephalosporin, and aminoglycoside in 4 cases; and a macrolide, cephalosporin, and carbapenem in 4 cases.

In antibiotic treatment of MAC (n=17), 13 patients were treated with a macrolide and 11 were treated with at least one HRZE medication (rifampin n=10, ethambutol n=8, isoniazid n=4). In treatment of *M. abscessus* (n=5), clarithromycin was used in all cases, 4 of 5 were treated with amikacin, and 3 of 5 treated with ciprofloxacin. In treatment of *M. fortuitum*, 3 of 4 patients received amikacin, but no other medication classes were shared across patients.

Non-Pharmaceutical Therapies and Procedures

In addition to medical therapy, several of the infants included in this study received additional therapy or underwent other therapeutic or diagnostic procedures. Of the 33 infants, 85% (n=28) underwent some sort of procedure. Among those procedures, the most common procedure was a diagnostic bronchoscopy with 79% (n=26) of infants receiving a bronchoscopy. Moreover, 39% (n=13) received debulking therapy or removal of granulation tissue. Furthermore, an additional 33% (n=11) of infants had a surgical biopsy to assist with confirmation of NTM diagnosis. Only 12% (n=4) of infants had a pneumonectomy, lobectomy, or other lung resection. Procedure data is summarized in [Figure 2](#). Other supportive therapies following NTM diagnosis included non-invasive supplemental oxygen (12%, n=4), and mechanical ventilation (6%, n=2). Additionally, three patients (9%, n=3) were admitted to an intensive care unit, and two (6%, n=2) patients were placed into a negative pressure isolation room.

Discussion

Our study focused on the therapeutic interventions of NTM pulmonary infections among infants. This study contributes new knowledge in the area of treatment of NTM pulmonary infections among this study group.

With regard to treatment regimens, recommendations for the total length of pulmonary NTM therapy in adults is at least 12 months of treatment with at least three active drugs, of which one should be azithromycin or clarithromycin.^{48,49} In our sample, published treatment durations were generally shorter (median 30 weeks), although cases did publish treatment of up to 9 years, which may capture variability in clinicians' decisions to end therapy in infants sooner following resolution of symptoms or negative cultures. Duration of therapy should be considered as infants may be susceptible to developmental impacts of prolonged antibiotic use that adult patients are not.^{50–52}

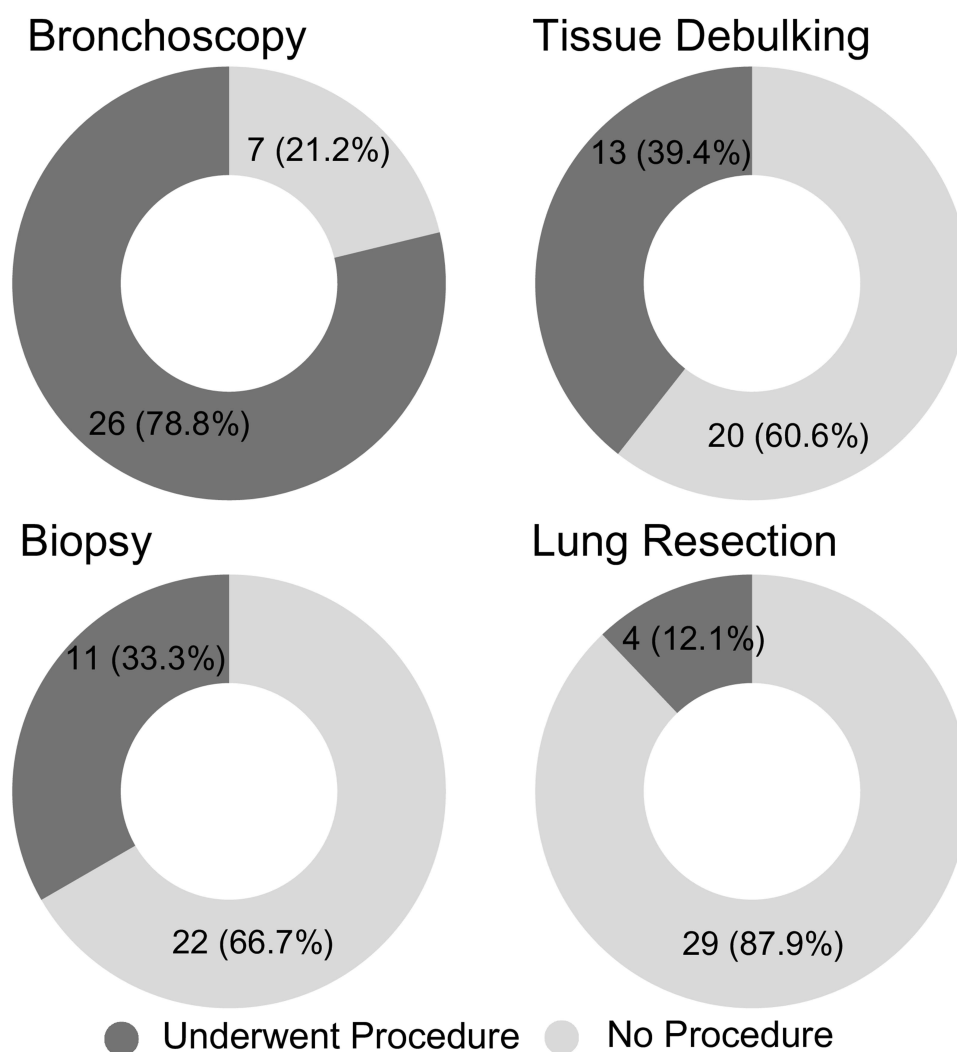


Figure 2 Procedures Performed on Infants.

Guidelines for the treatment of pulmonary NTM are largely empirical, and specific recommendations exist for some but not all strains of disease-causing NTM species.^{48,53,54} The commonly administered classes of antibiotics in our sample are reflective of these guidelines, with antibiotic therapy utilized in the majority of cases in our study (94%). Of studies reporting medications started before a diagnosis of NTM infection was made, the majority (86%) documented initiation of HRZE therapy for presumed tuberculosis, further highlighting the diagnostic challenge of distinguishing tuberculosis from pulmonary NTM infection on differential. The proportion of patients receiving antituberculous therapy after NTM diagnosis decreased (45%), which may reflect the mixed susceptibility of some but not all strains to rifampin, ethambutol, and/or isoniazid, with updated ATS/IDSA guidelines recommending these medications as part of multi-drug therapy in some cases.⁴⁸ Macrolides (n=23), aminoglycosides (n=11), and quinolones (n=9) were other commonly prescribed antibiotic classes in our patient sample. Overall, these trends are also reflected in the relative frequency with which these drug classes were prescribed together. Although clarithromycin was the most administered macrolide in our sample, ATS/IDSA guidelines conditionally suggest azithromycin-based over clarithromycin-based regimens for the treatment of pulmonary NTM. The higher proportion of treatment with these medications is of note as drug-resistance genes in NTM are also most commonly associated with resistance to macrolides and aminoglycosides.⁵⁵ Other studies have demonstrated that combined macrolide and fluoroquinolone therapy is associated with higher resistance, while macrolide, rifampin, and ethambutol combinations are associated with lower rates of culture conversion and treatment failure.^{56,57}

M. abscessus infection in particular has been documented as resistant to antibiotic therapy and sputum conversion among adults with pulmonary NTM infection, with a lower cure rate compared to MAC pulmonary disease.⁵³ In our sample, all infants diagnosed with *M. abscessus* (n=5) survived and were considered by case authors to be successfully managed, although 2 cases did not describe long-term culture results. Of the mycobacterial strains discussed in this paper, Meoli et al note that *M. abscessus* exhibits extensive antibiotics resistance in the pediatric population due to its full-length erm(41) gene expression, necessitating careful antibiotic selection—especially for macrolides—to avoid treatment failure.⁵⁸

We have previously reported that *Mycobacterium avium* complex (MAC) was the most common species responsible for infection in a population similar to the current sample,²¹ which is consistent with previous literature on pulmonary NTM infections in immunocompromised patients.⁵⁹ *M. abscessus* and *M. fortuitum* were the next most common species in our sample (18% and 12% respectively), which are also commonly identified disease-causing strains in previous epidemiologic studies, although relative proportions vary by geography.⁶

The clinical course of NTM pulmonary infections was characterized by prolonged hospital stay (median 25 days; IQR 14–112), indicative of the complicated factors affecting NTM infection diagnosis and treatment in infants. The length of hospitalization may reflect the severity of disease, but also the diagnostic uncertainty associated with pulmonary NTM infections. Due to its similarity in clinical presentation to tuberculosis, NTM pulmonary infections are frequently misdiagnosed in early stages, which can delay appropriate treatment and complicate patient outcomes.⁶⁰ Positive acid-fast staining of sputum smears can increase suspicion for NTM pulmonary disease that requires treatment, but limitations include inability of this test to differentiate between *M. tuberculosis* and NTM as well as reported variable sensitivity and limited use in paucibacillary populations, such as pediatric patients.⁶¹ Molecular methods are recommended to aid in NTM detection, differentiation from *M. tuberculosis*, and NTM species identification, but access to these tests can be limited in low-resource settings and can similarly be limited by lower bacterial levels in pediatric mycobacterial infections.⁶² Additionally, our previous work in a similar population of infants showed that published case reports on pulmonary NTM infections turned positive acid-fast bacilli staining in only about half of cases tested, and that tuberculin skin tests returned positive results in 9 out of 22 cases, further highlighting the need for careful clinical consideration to make a pulmonary NTM diagnosis.²¹ Growth of NTM from respiratory specimen alone is not sufficient to diagnose NTM as the causative agent of infection, both due to the possibility of environmental contamination and because not all respiratory NTM growth is associated with progressive disease.⁴⁸ Instead, radiographic and clinical criteria must also be fulfilled, and multiple positive cultures across time are also recommended, increasing the time required to make a diagnosis.

Although procedures for the purpose of diagnosis were common in this sample as well as a similar previous sample that included immunocompromised infants,²¹ procedural interventions intended for treatment of nontuberculous mycobacterial infections were infrequent and generally reserved for specific clinical scenarios such as hemoptysis or severe bronchiectasis, as they were only utilized in 12% (n=4) of the patients included in this study. ATS guidelines suggest that the cure rate for NTM was not statistically significant when comparing patients treated with antibiotics alone compared to patients treated with both antibiotics and surgery. Additionally, per ATS guidelines, surgical complications were observed in 7–35% of patients who received surgery, underscoring the limited role of surgical interventions in the management of NTM infections.⁴⁸ Furthermore, Lu et al also report that early post-surgical mortality for NTM treatment is low, while long-term mortality—measured between 6 and 8 years—can vary widely between 3% and 21%. However, there is a dearth of specific information regarding surgery for pulmonary NTM among children.⁶³ Furthermore, given that lymphadenitis is the most common clinical manifestation of NTM disease in immunocompetent children, it is important to note that surgical excision of affected lymph nodes is preferred treatment.⁵⁸ Given the pediatric population of this study, high long-term post-surgical mortality should be considered as a critical factor when evaluating the risk-benefit ratio of surgical interventions, as it may influence the decision to prioritize less invasive treatments and focus on optimizing antibiotic regimens tailored to the specific needs of younger patients.

Key limitations of this study include its retrospective design and the heterogeneous nature of case reports and case series from which data was extracted. Included studies may have been written and published upon discharge from the hospital or apparent resolution of clinical symptoms, limiting this study's ability to report on long-term patient outcomes. Mortality outcomes and duration of antibiotic therapy may be biased by lack of reporting of complete outpatient antibiotics regimens and adjustments, long-term complications, rehospitalizations, or deaths

that occurred after patients' apparent improvement at the time of discharge and case report preparation. The results of this study should be interpreted in this context. Despite these limitations, the management data presented in this paper is of relevance for contextualizing existing treatment strategies in a specific subset of patients with this uncommon infection, especially given the empiric nature of pulmonary NTM treatment. Further investigations through retrospective chart review and prospective study designs are warranted to more fully characterize management, long-term followup, and outcomes among this population.

Conclusions

This review is the first to our knowledge to address and review the complexity of managing pulmonary NTM infections in immunocompetent infants and to describe the diverse therapeutic approaches with varying antibiotic use and procedural interventions present in the existing literature. Our findings underscore the reliance on antibiotic therapy as the cornerstone of present treatment practices, where macrolides paired with quinolones, aminoglycosides paired with cephalosporins, and combined ethambutol and rifampin were among the most common combinations administered. Nonetheless, antibiotic regimens were highly variable with no combinations being administered to more than a third of our sample, which reflects the absence of tailored pediatric-specific guidelines that can be applied to this population. Procedural interventions were less commonly utilized but have also been documented as successful adjuvant management options, or even as the sole treatment technique in rare cases. Supplemental therapies were infrequently reported in the literature.

The retrospective nature of this review, drawn from disparate case studies and series, limits the generalizability of findings and underscores the need for standardized data collection and reporting in future studies. Despite these limitations, this analysis serves as a foundational step in addressing the knowledge gap regarding the management of pulmonary NTM infections in immunocompetent infants. The treatment modalities reported in this study may provide a baseline of existing evidence for clinicians to consider in the management of patients with this disease in the absence of population-specific guidelines based on observational and experimental studies among otherwise healthy infants. Future research, especially prospective and randomized controlled trials, to investigate relative efficacy of different antibiotics, treatment regimens, and long-term outcomes is necessary to refine treatment guidelines, optimize outcomes, and mitigate risks in this vulnerable patient population.

Abbreviation

NTM, Nontuberculous mycobacteria.

Acknowledgments

The authors would like to thank Insmad for providing funds to support this study. The authors would like to thank Rady Children's Hospital Health Sciences Library services for their expertise. Data from this paper was presented at *CHEST 2024* as an abstract presentation with interim findings. The poster's abstract was published in "Chest Infections Abstracts Posters" in *CHEST*:10.1016/j.chest.2024.06.805.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Koh WJ. Nontuberculous mycobacteria—overview. *Microbiol Spectr*. 2017;5(1):10.1128/microbiol-spec.tnmi7-0024-2016. doi:10.1128/microbiol-spec.tnmi7-0024-2016
2. Henkle E, Winthrop K. Nontuberculous mycobacteria infections in immunosuppressed hosts. *Clin Chest Med*. 2015;36(1):91–99. doi:10.1016/j.ccm.2014.11.002
3. Dahl VN, Mølhave M, Fløe A, et al. Global trends of pulmonary infections with nontuberculous mycobacteria: a systematic review. *Int J Infect Dis*. 2022;125:120–131. doi:10.1016/j.ijid.2022.10.013
4. Hill AR. The quest for systematic epidemiology of nontuberculous mycobacterial lung disease in the United States: closing in on an elusive goal. *Ann Am Thorac Soc*. 2020;17(2):169–172. doi:10.1513/AnnalsATS.201911-846ED

5. Prevots DR, Marshall JE, Wagner D, Morimoto K. Global epidemiology of nontuberculous mycobacterial pulmonary disease: a review. *Clin Chest Med.* 2023;44(4):675–721. doi:10.1016/j.ccm.2023.08.012
6. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. *Clin Chest Med.* 2015;36(1):13–34. doi:10.1016/j.ccm.2014.10.002
7. Abidin NZ, Gardner AI, Robinson HL, Haq IJ, Thomas MF, Brodlie M. Trends in nontuberculous mycobacteria infection in children and young people with cystic fibrosis. *J Cyst Fibros.* 2021;20(5):737–741. doi:10.1016/j.jcf.2020.09.007
8. Dolezalova K, Maly M, Wallenfels J, Gopfertova D. Nontuberculous mycobacterial infections in children in the Czech Republic in the period 2003–2018. *Biomed Pap.* 2021;165(3):277–282. doi:10.5507/bp.2020.025
9. Ford TJ, Silcock RA, Holland SM. Overview of nontuberculous mycobacterial disease in children. *J Paediatr Child Health.* 2021;57(1):15–18. doi:10.1111/jpc.15257
10. Yang B, Jhun BW, Moon SM, et al. Clofazimine-containing regimen for the treatment of *Mycobacterium abscessus* lung disease. *Antimicrob Agents Chemother.* 2017;61(6):e02052–16. doi:10.1128/AAC.02052-16
11. Bhattacharya J, Mohandas S, Goldman DL. Nontuberculous mycobacterial infections in children. *Pediatr Rev.* 2019;40(4):179–190. doi:10.1542/pir.2018-0131
12. Nontuberculous mycobacterial pulmonary infections in children - UpToDate. Available from: <https://www.uptodate.com/contents/nontuberculous-mycobacterial-pulmonary-infections-in-children>. Accessed July 07, 2025.
13. Dou W, Xin L, Pengjiao A, Wei Z, Zhang B. Real-world safety profile of tetracyclines in children younger than 8 years old: an analysis of FAERS database and review of case report. *Expert Opin Drug Saf.* 2024;23(7):885–892. doi:10.1080/14740338.2024.2359615
14. Han S, Mallampalli RK. The role of surfactant in lung disease and host defense against pulmonary infections. *Ann Am Thorac Soc.* 2015;12(5):765–774. doi:10.1513/AnnalsATS.201411-507FR
15. van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol.* 2018;58(S10):S10–S25. doi:10.1002/jcph.1284
16. Matsuyama M, Matsumura S, Nonaka M, et al. Pathophysiology of pulmonary nontuberculous mycobacterial (NTM) disease. *Respir Investig.* 2023;61(2):135–148. doi:10.1016/j.resinv.2022.12.002
17. Aloisio GM, Nagaraj D, Murray AM, et al. Infant-derived human nasal organoids exhibit relatively increased susceptibility, epithelial responses, and cytotoxicity during RSV infection. *J Infect.* 2024;89(6):106305. doi:10.1016/j.jinf.2024.106305
18. Upham JW, Lee PT, Holt BJ, et al. Development of interleukin-12-producing capacity throughout childhood. *Infect Immun.* 2002;70(12):6583–6588. doi:10.1128/IAI.70.12.6583-6588.2002
19. PRISMA statement. PRISMA statement. Available from: <https://www.prisma-statement.org>. Accessed July 07, 2025.
20. Hardin AP, Hackell JM, Simon GR, et al. Committee on Practice and Ambulatory Medicine. Age limit of pediatrics. *Pediatrics.* 2017;140(3):e20172151. doi:10.1542/peds.2017-2151
21. Bai A, Belda O, Dosanjh A. Pulmonary nontuberculous mycobacterial infection in infants: a systematic review. *Pediatr Health Med Ther.* 2021;12:551–559. doi:10.2147/PHMT.S332434
22. Alramadhan MM, Murphy JR, Chang ML. Extensive *Mycobacterium abscessus* pneumonia in an immunocompetent infant with no underlying lung pathology. *Case Rep Infect Dis.* 2021;2021:6615722. doi:10.1155/2021/6615722
23. Annobil SH, Jamjoom GA, Bobo R, Iyengar J. Fatal lipoid pneumonia in an infant complicated by *Mycobacterium fortuitum* infection. *Trop Geogr Med.* 1992;44(1–2):160–164.
24. Del Rio Camacho G, Soriano Guillén L, Flandes Aldeyturriaga J, Hernández García B, Bernácer Borja M. Endobronchial atypical mycobacteria in an immunocompetent child. *Pediatr Pulmonol.* 2010;45(5):511–513. doi:10.1002/ppul.21194
25. PCM D, Nussbaum E, Moua J, Chin T, Randhawa I. Clinical significance of respiratory isolates for *Mycobacterium abscessus* complex from pediatric patients. *Pediatr Pulmonol.* 2013;48(5):470–480. doi:10.1002/ppul.22638
26. Eneli I, West M, Sigal Y, et al. Index of suspicion. *Pediatr Rev.* 2006;27(10):389–394. doi:10.1542/pir.27-10-389
27. Freeman AF, Olivier KN, Rubio TT, et al. Intrathoracic nontuberculous mycobacterial infections in otherwise healthy children. *Pediatr Pulmonol.* 2009;44(11):1051–1056. doi:10.1002/ppul.21069
28. Glatstein M, Scolnik D, Bensira L, Domany KA, Shah M, Vala S. Lung abscess due to non-tuberculous, non-*Mycobacterium fortuitum* in a neonate. *Pediatr Pulmonol.* 2012;47(10):1034–1037. doi:10.1002/ppul.22558
29. Gupta SK, Katz BZ. Intrathoracic disease associated with *Mycobacterium avium*-intracellular complex in otherwise healthy children: diagnostic and therapeutic considerations. *Pediatrics.* 1994;94(5):741–742. doi:10.1542/peds.94.5.741
30. Jamal W, Salama MF, Al Hashem G, et al. An outbreak of *Mycobacterium abscessus* infection in a pediatric intensive care unit in Kuwait. *Pediatr Infect Dis J.* 2014;33(3):e67–70. doi:10.1097/INF.0000000000000071
31. Kröner C, Griesse M, Kappler M, et al. Endobronchial lesions caused by nontuberculous mycobacteria in apparently healthy pediatric patients. *Pediatr Infect Dis J.* 2015;34(5):532–535. doi:10.1097/INF.0000000000000606
32. Kumar KJ, Chandra J, Mandal RN, Dutta R, Jain NK. Fatal pulmonary infection caused by *Mycobacterium smegmetis* in an infant. *Indian J Pediatr.* 1995;62(5):619–621. doi:10.1007/BF02761893
33. Leitritz L, Griesse M, Roggenkamp A, Geiger AM, Fingerle V, Heesemann J. Prospective study on nontuberculous mycobacteria in patients with and without cystic fibrosis. *Med Microbiol Immunol.* 2004;193(4):209–217. doi:10.1007/s00430-003-0195-9
34. Levrey-Hadden H, Reix P, Louis D, Bellon G. Non-tuberculous mycobacterial lung infection mimicking primary tuberculosis in non-immunocompromised children. *Acta Paediatr Oslo nor* 1992. 2002;91(6):725–726. doi:10.1111/j.1651-2227.2002.tb03313.x
35. Lewis CR, Carroll V. Not all that wheezes is asthma. *Clin Pediatr.* 2014;53(7):708–709. doi:10.1177/0009922814526989
36. Liu H, Dong F, Liu J, et al. Successful management of *Mycobacterium abscessus* complex lung disease in an otherwise healthy infant. *Infect Drug Resist.* 2019;12:1277–1283. doi:10.2147/IDR.S198461
37. Nolt D, Michaels MG, Wald ER. Intrathoracic disease from nontuberculous mycobacteria in children: two cases and a review of the literature. *Pediatrics.* 2003;112(5):e434. doi:10.1542/peds.112.5.e434
38. Osorio A, Kessler RM, Guruprasad H, Isaacson G. Isolated intrathoracic presentation of *Mycobacterium avium* complex in an immunocompetent child. *Pediatr Radiol.* 2001;31(12):848–851. doi:10.1007/s002470100003

39. Paone RF, Mercer LC, Glass BA. Pneumonectomy secondary to *Mycobacterium fortuitum* in infancy. *Ann Thorac Surg*. 1991;51(6):1010–1011. doi:10.1016/0003-4975(91)91036-u
40. Perisson C, Nathan N, Thierry B, Corvol H. Endobronchial avium mycobacteria infection in an immunocompetent child. *BMJ Case Rep*. 2013;2013:bcr2013200776. doi:10.1136/bcr-2013-200776
41. Piedimonte G, Wolford ET, Fordham LA, Leigh MW, Wood RE. Mediastinal lymphadenopathy caused by *Mycobacterium avium*-intracellulare complex in a child with normal immunity: successful treatment with anti-mycobacterial drugs and laser bronchoscopy. *Pediatr Pulmonol*. 1997;24(4):287–291. doi:10.1002/(sici)1099-0496(199710)24:4<287::aid-ppul8>3.0.co;2-h
42. Sands A, Klepper E, Bolton M. *Mycobacterium abscessus* pneumonia in an immunonormal infant. *Pediatr Infect Dis J*. 2022;41(12):e537–e539. doi:10.1097/INF.0000000000003681
43. Sankar J, Piduru P. Atypical presentation of atypical organism. *Indian Pediatr*. 2007;44(2):151.
44. Shanthikumar S, Lwin T, Chow CW, Cramer J, Harrison J. A toddler with a cough and wheeze refractory to treatment. *Thorax*. 2017;72(10):953–955. doi:10.1136/thoraxjnl-2016-209915
45. Sharma D, Hilinski JA. Refractory pneumonia in a Mexican American infant. *Clin Pediatr*. 2010;49(7):710–712. doi:10.1177/000922808325462
46. Sparks JD, Das BB, Eid NS, Austin EH, Recto M. Atypical mycobacterial infection in sequestered lung in an infant presenting with chronic pneumonitis and recurrent wheezing. *Congenit Heart Dis*. 2008;3(4):284–287. doi:10.1111/j.1747-0803.2008.00182.x
47. Tuerlinckx D, Bodart E, Lacrosse M, de Bilderling G. Pulmonary disease possibly caused by *Mycobacterium avium* in an HIV-negative infant. *Eur J Pediatr*. 2000;159(3):225–226. doi:10.1007/s004310050058
48. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J*. 2020;56(1):2000535. doi:10.1183/13993003.00535-2020
49. Lange C, Böttger EC, Cambau E, et al. Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases. *Lancet Infect Dis*. 2022;22(7):e178–e190. doi:10.1016/S1473-3099(21)00586-7
50. Aversa Z, Atkinson EJ, Schafer MJ, et al. Association of infant antibiotic exposure with childhood health outcomes. *Mayo Clin Proc*. 2021;96(1):66–77. doi:10.1016/j.mayocp.2020.07.019
51. Shekhar S, Petersen FC. The dark side of antibiotics: adverse effects on the infant immune defense against infection. *Front Pediatr*. 2020;8:544460. doi:10.3389/fped.2020.544460
52. Duong QA, Pittet LF, Curtis N, Zimmermann P. Antibiotic exposure and adverse long-term health outcomes in children: a systematic review and meta-analysis. *J Infect*. 2022;85(3):213–300. doi:10.1016/j.jinf.2022.01.005
53. Wu ML, Aziz DB, Dartois V, Dick T. NTM drug discovery: status, gaps and the way forward. *Drug Discov Today*. 2018;23(8):1502–1519. doi:10.1016/j.drudis.2018.04.001
54. Haworth CS, Banks J, Capstick T, et al. British thoracic society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax*. 2017;72(Suppl 2):ii1–ii64. doi:10.1136/thoraxjnl-2017-210927
55. Solanki P, Lipman M, McHugh TD, Satta G. Whole genome sequencing and prediction of antimicrobial susceptibilities in non-tuberculous mycobacteria. *Front Microbiol*. 2022;13:1044515. doi:10.3389/fmicb.2022.1044515
56. Griffith DE, Brown-Elliott BA, Langsjoen B, et al. Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med*. 2006;174(8):928–934. doi:10.1164/rccm.200603-450OC
57. Jeong BH, Jeon K, Park HY, et al. Intermittent antibiotic therapy for nodular bronchiectatic *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med*. 2015;191(1):96–103. doi:10.1164/rccm.201408-1545OC
58. Meoli A, Deolmi M, Iannarella R, Esposito S. Non-tuberculous mycobacterial diseases in children. *Pathogens*. 2020;9(7):553. doi:10.3390/pathogens9070553
59. Koh WJ, Kwon OJ, Lee KS. Nontuberculous mycobacterial pulmonary diseases in immunocompetent patients. *Korean J Radiol*. 2002;3(3):145–157. doi:10.3348/kjr.2002.3.3.145
60. Kendall BA, Varley CD, Choi D, et al. Distinguishing tuberculosis from nontuberculous mycobacteria lung disease, Oregon, USA. *Emerg Infect Dis*. 2011;17(3):506–509. doi:10.3201/eid1703.101164
61. Forbes BA, Hall GS, Miller MB, et al. Practical guidance for clinical microbiology laboratories: mycobacteria. *Clin Microbiol Rev*. 2018;31(2):10.1128/cmr.00038–17. doi:10.1128/cmr.00038-17
62. López-Varela E, García-Basteiro AL, Santiago B, Wagner D, Kampmann B, Kampmann B. Non-tuberculous mycobacteria in children: muddying the waters of tuberculosis diagnosis. *Lancet Respir Med*. 2015;3(3):244–256. doi:10.1016/S2213-2600(15)00062-4
63. Lu M, Fitzgerald D, Karpelowsky J, et al. Surgery in nontuberculous mycobacteria pulmonary disease. *Breathe*. 2018;14(4):288–301. doi:10.1183/20734735.027218

Pediatric Health, Medicine and Therapeutics

Publish your work in this journal

Pediatric Health, Medicine and Therapeutics is an international, peer-reviewed, open access journal publishing original research, reports, editorials, reviews and commentaries. All aspects of health maintenance, preventative measures and disease treatment interventions are addressed within the journal. Practitioners from all disciplines are invited to submit their work as well as healthcare researchers and patient support groups. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/pediatric-health-medicine-and-therapeutics-journal>

Dovepress
Taylor & Francis Group