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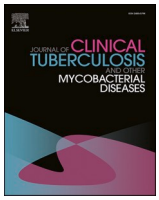

Clinical pharmacists' interventions and therapeutic drug monitoring in patients with mycobacterial infections

Anna M. Woods [a], Kristin C. Mara [b], Christina G. Rivera [a,*]

[a] Department of Pharmacy, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States
[b] Division of Biomedical Statistics and Informatics, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States

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ABSTRACT

Purpose: Infections caused by non-tuberculous mycobacterium (NTM) are increasing, less well-known by health care clinicians, and usually require long term treatment with multiple antimicrobials. There is no existing evidence on clinical pharmacists' involvement in the care of patients with NTM infections. We sought to characterize pharmacists' interventions in providing medication management for patients with NTM infections.

Methods: A retrospective review of patients aged 18 years or older seen by a pharmacist specializing in NTM from January 1, 2018 through June 1, 2020 was performed. Charts were reviewed for drug therapy problems identified by a pharmacist. Details regarding therapeutic drug monitoring (TDM) and subsequent dose adjustments were obtained.

Results: Seventy-seven patients were included. Median age was 68.5 years, and most patients were female. The most common mycobacterium species treated was *Mycobacterium avium/intracellulare complex*. Majority of pharmacist consults (63.6%) were referred by Pulmonology physicians, with remainder by Infectious Diseases clinicians. Identified drug therapy problems included: needs additional therapy (23%), unnecessary therapy (24.3%), different drug needed (6.8%), dose too low (75.7%), dose too high (20.3%), adverse drug reaction (31.1%), and adherence (8.1%). Fifteen patients had TDM performed during treatment. A clinical pharmacist was involved in evaluation of all TDM results. Over half of patients with TDM levels had at least 1 dose change made. A minority of patients (16.9%) experienced clinical failure.

Conclusion: Clinical pharmacists should be involved in this complex care to optimize medication management through identification of drug interactions, tailoring antimicrobial dosing, managing TDM results, and providing adherence counseling.

1. Background

While human infections due to *Mycobacterium tuberculosis* are well known by healthcare clinicians, lesser known are those caused by non-tuberculous mycobacteria (NTM), also known as mycobacterium other than tuberculosis. Similar to *Mycobacterium tuberculosis*, NTM infections can manifest in a number of different syndromes including skin and soft tissue infections and lymphadenitis, but most occur as pulmonary infection [1]. Treatment of mycobacterial infections involves complex, multidrug regimens taken for long periods of time that may be difficult to tolerate.

An interdisciplinary approach to optimize patient care outcomes should be utilized whenever the patient has a particularly complex disease state, or multiple medications are used to manage the condition. The Joint Commission of Pharmacy Practitioners describes a patient-centered care model where pharmacists collect and assess information from the patient, develop and implement a care plan in collaboration with the patient and other health care professionals, monitor the patient and potentially make changes to the plan in conjunction with the patient [2]. Some of the information gathered from the patient may include multiple drug therapy problems already present or would be introduced after initiation of a multiple drug regimen. Westberg et al describe several types of drug therapy problems that were divided into 7 classes: needs additional therapy, unnecessary drug therapy, different drug needed, dose too low, adverse drug reaction, dose too high, and adherence (Appendix A) [3]. Pharmacists then make recommendations based on the types of drug therapy problems to optimize patient outcomes. Since 2006 at our institution, ambulatory care based clinical

* Corresponding author.
E-mail addresses: Woods.Anna@mayo.edu (A.M. Woods), Mara.kristin@mayo.edu (K.C. Mara), rivera.christina@mayo.edu (C.G. Rivera).

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pharmacists have been consulted in the care of patients with mycobacterial disease in the Infectious Diseases/NTM clinic. Common pharmacists' interventions include adherence counseling, drug dosing review, drug interaction screening, and assistance with therapeutic drug monitoring (TDM) ordering and result assessment for both oral and intravenous therapies. Pharmacist face-to-face clinic visits and video visits for NTM were billed to insurance using incident-to or medication therapy management billing codes per our institutional ambulatory pharmacists group standards.

In the treatment of NTM, TDM of oral agents is less well established. However, consideration should be given to optimizing drug exposure and minimizing toxicity through serum level assessment given the extended duration of antimicrobial treatment. Charles Peloquin, PharmD, provides a detailed review of TDM in the setting of NTM disease [4]. While no clinical trials have fully determined the clinical utility of TDM results to guide NTM therapy, studies have documented significant drug interactions between clarithromycin and rifampin, and to a lesser extent with rifabutin, with the rifamycins significantly decreasing the serum concentrations of the macrolide [5]. One study showed no difference in treatment outcomes based on serum concentration of clarithromycin [6], while a second study did note a correlation between peak concentrations of azithromycin and favorable treatment outcomes with daily administration of azithromycin [7]. Other patient specific factors can be an indication for TDM. While TDM of oral antimicrobials is not standard of care for all patients, it may be considered in the following circumstances: concern for adequate drug absorption (surgical history of Roux-En-Y, graft versus host disease of the gut, severe gastrointestinal disease such as Crohn's disease), drug interactions where increased or decreased antimicrobial exposure is expected, renal/hepatic dysfunction, or lack of clinical/microbiological response to therapy [4]. There is currently no standard approach to patient selection for NTM TDM at our institution; rather, it is assessed by clinicians on a case-by-case basis. Further, the latest released ATS/IDSA guidelines for the treatment of pulmonary mycobacterial disease does not provide firm guidance regarding TDM, but gives clinical scenarios when a clinician may consider TDM [5].

There is also little evidence on patient outcomes when a clinical pharmacist is involved in the treatment of NTM infection to TDM management in this setting. At our institution, the usual process involves the pharmacist ordering 2- and 6-hour post dose levels for each oral NTM drug as has been described by Charles Peloquin [4]. The blood samples are sent to an external institution for oral NTM drug serum assays to be performed. For intravenous amikacin, a trough, 2- and 6-hour post end of infusion levels are obtained initially. After an estimated goal peak is obtained, then trough only monitoring is continued once weekly throughout therapy. Amikacin serum assay testing is performed internally. Once available, the results are reviewed and interpreted by a clinical pharmacist. Pharmacist recommendations are documented in the electronic medical record and communicated to the treating physician.

We sought to characterize clinical pharmacist interventions in providing medication management services for patients with NTM infections including involvement with TDM.

2. Methods

This study was a single-site, retrospective chart review of Mayo Clinic Rochester patients with mycobacterial infection referred to an ambulatory care clinical pharmacist between January 1, 2018 and June 1, 2020. This study was deemed exempt by a local Institutional Review Board (approval number 20–004605).

2.1. Patient population

To be included, patients needed to be adults aged 18 years or older, seen in the outpatient setting by a pharmacist face-to-face in the outpatient Infectious Diseases clinic or by telephonic visit, video visit, or e-consult, and had at least two anti-mycobacterial medications initiated for treatment. Patients were excluded if they were pregnant or breast-feeding, incarcerated, had no Minnesota research authorization on file, had a diagnosis of NTM and treated with pulmonary hygiene and/or surgical treatment only or were not seen by a clinical pharmacist. A report was generated of NTM consult pharmacist visits for inclusion screening and data abstraction was performed via manual chart review.

2.2. Outcomes

The primary outcome was to characterize the number of drug therapy problems identified by the clinical pharmacist. Secondary outcomes included determining the percent of patients that received TDM and had a dose change based on the TDM results, and rate of clinical failure in patients without TDM results. Patients with documentation in the progress note of worsening NTM related symptoms and/or escalation of treatment by the physician during NTM clinic follow up were considered clinical failure for the purposes of this study.

2.3. Statistical analysis

Only investigators directly involved in collection and analysis of data had access. Statistics were descriptive in nature, with mean or median reported as pertinent. Study data were recorded and managed using the Research Electronic Data Capture system [8].

3. Results

Between January 1, 2018 and June 1, 2020, there were 77 patient clinic-based encounters with an ambulatory care based clinical pharmacist. Of those, 40% of patients had repeat contact with a pharmacist regarding NTM treatment, ranging from 1 to 16 follow up phone calls and/or electronic messages per patient. During the study time frame, there were 113 new physician consults to the NTM clinic. Pharmacist consults were referred by Pulmonology physicians in 63.6% of patients, and the remainder by Infectious Diseases physicians and advanced practice providers. Median age of the patients seen by the clinical pharmacist was 68.5 years, and 71.4% of patients were female (Table 1). The most common NTM infection that patients had was pulmonary in nature. Other types of NTM infection included skin and soft tissue, bone and joint, cervical lymphadenitis, and disseminated. The most common NTM species treated was *Mycobacterium avium/intracellulare complex* (81.8%, 63/77 patients), with the second most common species treated was *Mycobacterium abscessus complex* (14.3%, 11/77 patients). Most patients utilized the following medications in their regimen: ethambutol (64 patients), azithromycin (57 patients), and rifampin (49 patients) (Table 2). Most patients had a once daily regimen, while a fourth of patients took medications three times weekly. All patients utilized a regimen of at least 2 antibiotics for NTM treatment, with most patients using 3 antibiotics. There were 13 patients (12.9%) with NTM clinical failure (11 pulmonary and 2 skin and soft tissue infections) with 5 patients (6.5%) lost to follow up in the entire cohort.

3.1. Drug therapy problems identified by a pharmacist

Most patients had at least 1 drug therapy problem identified by the clinical pharmacist (96%) (Fig. 1). There was a total of 245 drug therapy problems identified in this cohort of patients. The most common drug therapy problem categories were dose too low, adverse drug reaction, and unnecessary therapy (Fig. 2). Dose too low was attributed to drug interactions in 71.4% of drug therapy problems and rifampin was the NTM medication implicated in 57.1% of the drug interactions. Only 16 patients had no drug interactions identified during the appointment. The second most common drug therapy problem identified was adverse drug reaction, seen in 23 patients, attributed to drug interactions in 8 cases

Table 1
Patient Characteristics.

	Level Drawn (N = 15)	No Level Drawn (N = 62)	Total (N = 77)
Age (Median, IQR)	68 (57, 75.8)	68.7 (62.4, 73)	68.5 (62.2, 73)
Gender, N (%)			
Male	5 (33.3)	17 (27.4)	22 (28.6)
Female	10 (66.7)	45 (72.6)	55 (71.4)
Type of Insurance, N (%)			
Commercial	5 (33.3)	21 (33.9)	26 (33.8)
Medicare / Medicaid	10 (66.7)	40 (64.5)	50 (64.9)
Other	0 (0)	1 (1.6)	1 (1.3)
Referring Provider, N (%)			
Infectious Disease	10 (66.7)	18 (29)	28 (36.4)
Pulmonary Medicine	5 (33.3)	44 (71)	49 (63.6)
NTM Infection Type, N (%)			
Pulmonary	12 (80)	52 (83.9)	64 (83.1)
Skin and soft tissue	3 (20)	3 (4.8)	6 (7.8)
Bone and joint	0 (0)	5 (8.1)	5 (6.5)
Cervical lymphadenitis	0 (0)	1 (1.6)	1 (1.3)
Disseminated	0 (0)	1 (1.6)	1 (1.3)
NTM Species, N (%)			
M. avium/intracellulare complex	9 (47.4)	54 (75)	63 (69.2)
M. abscessus complex	6 (31.6)	5 (6.9)	11 (12.1)
M. arupense	2 (10.5)	0 (0)	2 (2.2)
M. chelonae	0 (0)	3 (4.2)	3 (3.3)
M. chimera	1 (5.3)	1 (1.4)	2 (2.2)
M. cosmeticum	1 (5.3)	0 (0)	1 (1.1)
M. frederiksbergense	0 (0)	1 (1.4)	1 (1.1)
M. kansasii	0 (0)	4 (5.6)	4 (4.4)
M. lentiflavum	0 (0)	1 (1.4)	1 (1.1)
M. shimoidei	0 (0)	1 (1.4)	1 (1.1)
M. szulgai	0 (0)	2 (2.8)	2 (2.2)

IQR = interquartile range; NTM = non-tuberculous mycobacterium.

Table 2
Treatment Characteristics.

	Level Drawn (N = 15)	No Level Drawn (N = 62)	Total (N = 77)
NTM Regimen, N (%)			
Azithromycin oral	8 (16.3)	49 (26.8)	57 (24.7)
Clarithromycin oral	3 (6.1)	11 (6)	14 (6)
Rifampin oral	5 (10.2)	44 (24)	49 (21.1)
Rifabutin oral	5 (10.2)	8 (4.4)	13 (5.6)
Ethambutol oral	10 (20.4)	54 (29.5)	64 (27.6)
Amikacin IV	7 (14.3)	1 (0.5)	8 (3.4)
Amikacin inhaled liposomal	1 (2)	4 (2.2)	5 (2.2)
Amikacin inhaled non-liposomal	0 (0)	1 (0.5)	1 (0.4)
Imipenem IV	2 (4.1)	0 (0)	2 (0.9)
Tigecycline IV	2 (4.1)	2 (1.1)	4 (1.7)
Ciprofloxacin oral	0 (0)	1 (0.5)	1 (0.4)
Clofazimine oral	3 (6.1)	6 (3.3)	9 (3.9)
Linezolid oral	1 (2)	1 (0.5)	2 (0.9)
Cefoxitin IV	2 (4.1)	0 (0)	2 (0.9)
Tedizolid oral	0 (0)	1 (0.5)	1 (0.4)
Dose Frequency of NTM Regimen at Time of RPh Encounter, N (%)			
Once daily	12 (80)	42 (67.7)	54 (70.1)
Three times weekly	0 (0)	20 (32.3)	20 (26)
Other	3 (20)	0 (0)	3 (3.9)
Other Frequency, N (%)			
Amikacin TIW, tigecycline q24, imipenem q12	1 (33.3)	0	1 (33.3)
Amikacin TIW, tigecycline q24, cefoxitin q12	1 (33.3)	0	1 (33.3)
Twice daily (outside provider), changed to once daily prior to TDM	1 (33.3)	0	1 (33.3)
HIV Status, N (%)			
Yes	0 (0)	1 (1.6)	1 (1.3)
No	15 (100)	61 (98.4)	76 (98.7)

NTM = non-tuberculous mycobacterium; IV = intravenous; RPh = registered pharmacist; TIW = three times weekly; q24 = every 24 h; q12 = every 12 h; TDM = therapeutic drug monitoring.

(34.8%).

3.2. Therapeutic drug monitoring

Fifteen patients had TDM performed. In over half of these patients (8/15, 53.3%) at least one of the NTM antimicrobials required a dose change. The most common drugs having TDM resulting in dose adjustment were azithromycin and ethambutol. All TDM-based dose adjustments were dose increases, other than amikacin which resulted in both dose increases and decreases (Table 3). Some of the reasons for requesting TDM included: concern of adequate drug absorption (2 patients), adverse drug event or safety (4 patients), disease progression or continued microbiologic positivity (5 patients), drug interactions 2 patients), and lastly as standard monitoring for aminoglycosides (3 patients). An additional 2 patients were recommended to have serum drug levels drawn due to concerns of adequate drug absorption, but TDM was not performed. Recommendations for TDM came from both physicians and pharmacists. Of 6 patients who had serum drug levels checked again at a later date, only 1 patient required an additional dose change. Within the group of patients who had TDM analysis performed and had a dose change made as a result of the TDM results (8 patients) excluding patients taking amikacin IV, 1 patient still had clinical failure. In the group of patients who had TDM analysis performed and did not have a dose change made due to those results (7 patients), 3 patients experienced clinical failure. In the group of patients who did not undergo TDM analysis (62 patients), 8 patients had NTM disease clinical failure. Pharmacists were involved in the review of all TDM results and dose adjustment recommendations.

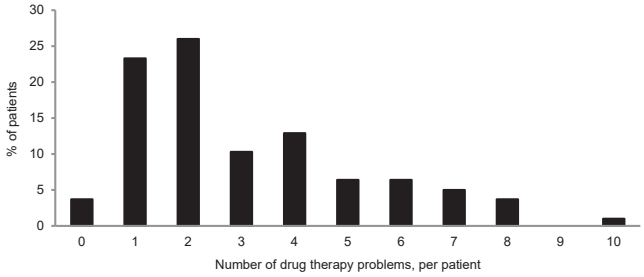

Fig. 1. Total number of drug therapy problems identified by the pharmacist, per patient. This shows the percentage of patients that had the indicated number of drug therapy problems.

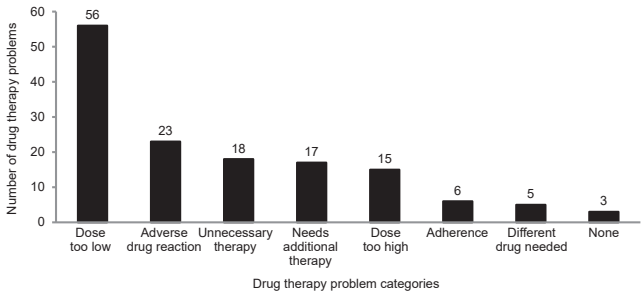

Fig. 2. Types of drug therapy problems identified in this patient cohort by the pharmacist and how many of each type of drug therapy problem was identified in the patient group.

4. Discussion

This is the first reported assessment of a clinical pharmacist service

Table 3
Therapeutic drug monitoring.

	Level Drawn (N = 15)
Recommendation for TDM from, N (%)	
Physician	9 (60.0)
Pharmacist	6 (40.0)
NTM Medications Recommended for TDM, N (%)	
Azithromycin oral	5 (33.3)
Rifampin oral	4 (26.7)
Rifabutin oral	5 (33.3)
Ethambutol oral	7 (46.7)
Amikacin IV	7 (46.7)
Clofazimine oral	2 (13.3)
Did TDM Result in Medication Dose Changes, N (%)	
Yes	8 (53.3)
No	7 (46.7)
Medication Dose Changed Due to TDM Results, N (%)	
Azithromycin oral, dose increased	3 (37.5) 7
Rifampin oral, dose increased	1 (12.5)
Rifabutin oral, dose increased	2 (25.0)
Ethambutol oral, dose increased	3 (37.5)
Amikacin IV, dose increased	1 (12.5)
Amikacin IV, dose decreased	2 (25.0)
N/A	7

TDM = therapeutic drug monitoring; IV = intravenous.

providing care to patients with NTM infections. We found that 96% of patients in our cohort had at least 1 drug therapy problem identified by the pharmacist. This is increased compared to Westberg et al. who identified at least 1 drug therapy problem in 89.5% of their patient population [3]. There did not appear to be a difference in drug therapy problem types identified between patients who had TDM performed versus patients who did not. Most of the drug therapy problems identified were potential issues based on the new antibiotics the patient would be starting for their NTM infection. Most patients are referred to our tertiary care center for NTM infection and receive primary care management elsewhere. Therefore, patients were advised to notify their local primary care provider of our recommendations regarding identified drug therapy problems involving their medications ancillary to NTM care, while TDM results and NTM medication dosing specifically was usually managed by the Infectious Diseases and/or Pulmonology teams including the pharmacist. Adverse events were co-managed episodically between pharmacists and physicians. We identified a high rate of repeat contact with pharmacists regarding NTM therapy, primarily patient questions regarding possible anti-mycobacterial adverse events. Patients were commonly advised to monitor for specific symptoms to signify if any medication changes needed to be made to their existing non-NTM medications by their primary care provider.

Nearly 20% of patients who were referred to the clinical pharmacist had TDM performed. Over half of these patients required a dose change to their NTM regimen as a result of TDM level analysis. All patients who had a dose change had TDM performed again and only 1 patient required an additional dose change at the second TDM analysis. Rates of clinical failure were similar in patients who had TDM level analysis compared to patients who did not. This differs from what Byeong-Ho Jeong et al. found, but our study is also much smaller [7]. This study also looked at several species of NTM while Byeong-Ho Jeong et al. focused on patients with pulmonary *Mycobacterium avium complex* [7].

While treatment of NTM is often handled by specialists at referral centers, the incidence of NTM infections is increasing worldwide. Localized pulmonology infection is most frequent, but disseminated infections are also on the rise due to the increased use of immunosuppression [9]. With NTM infections increasing, there is likely to be an even greater need for clinicians, including pharmacists, with knowledge in NTM pharmacotherapy at non-referral sites. Pharmacists providing medication management services for NTM can be integrated with Primary Care, Internal Medicine, Pulmonary medicine, or HIV/Infectious Diseases clinical services, as is the latter at our center.

Several limitations exist within this study. This study was limited to a single site with a small group of pharmacists who perform NTM management, thus limiting the generalizability of the results to all pharmacists. However, we believe that clinical pharmacists with medication management skills and education on NTM could reasonably offer these services. Our study was also underpowered to fully see if TDM analysis affected the clinical failure rate. Patients that did have TDM analysis performed tended to be more complex patients. This could introduce selection bias for patients that had TDM obtained to be more likely to have clinical failure. Due to the nature of our referral-based, destination medical center clinic and patients receiving primary care outside of our health system, the longitudinal impact and acceptance rate of pharmacists' interventions was not able to be assessed. Future directions could include incorporation of a collaborative practice agreement with all the referring clinician groups to facilitate pharmacist led NTM prescribing, lab monitoring, and more integrated long-term management.

5. Conclusion

Clinical pharmacists should be included in an interdisciplinary team and involved in the ambulatory care of patients with NTM disease, especially when TDM is being considered.

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CRediT authorship contribution statement

Anna M. Woods: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. **Kristin C. Mara:** Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Christina G. Rivera:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christina G Rivera reports a relationship with Insmed Inc. that includes: speaking and lecture fees.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2023.100346.

References

[1] Pennington KM, Vu A, Challener D, Rivera CG, Shweta FNU, Zeuli JD, et al. Approach to the diagnosis and treatment of non-tuberculous mycobacterial disease. J Clin Tuberc Other Mycobact Dis 2021;24:100244.
[2] Joint commission of Pharmacy Practitioners. Pharmacists' Patient Care Process. https://jcpp.net/ wp-content/uploads/2016/03/PatientCareProcess-with-supporting-organizations.pdf. Published May 29, 2014.

[3] Westberg SM, Derr SK, Weinhandl ED, Adam TJ, Brummel AR, Lahti J, et al. Drug therapy problems identified by pharmacists through comprehensive medication management following hospital discharge. J Pharm Technol 2017;33(3):96–107.
[4] Peloquin C, Schlossberg D. The role of therapeutic drug monitoring in mycobacterial infections. Microbiol Spectr 2017;5(1).
[5] Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATD/ERS/ESCMID/IDSA clinical practice guideline: executive summary. Clin Infect Dis 2020;ciaa214. https://doi.org/10.1093/cid/ciaa241.
[6] Koh W-J, Jeong B-H, Jeon K, Lee S-Y, Shin SJ. Therapeutic drug monitoring in the treatment of *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med 2012;186(8):797–802.
[7] Jeong B-H, Jeon K, Park HY, Moon SM, Kim S-Y, Lee S-Y, et al. Peak plasma concentration of azithromycin and treatment responses in *Mycobacterium avium* complex lung disease. Antimicrob Agents Chemother 2016;60(10):6076–83.
[8] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
[9] To K, Cao R, Yegiazaryan A, Owens J, Venketaraman V. General Overview of Nontuberculous Mycobacteria Opportunistic Pathogens: *Mycobacterium avium* and *Mycobacterium abscessus*. J Clin Med 2020;9(8):2541.