Retrospective Observational Study of Pulmonary Non-Tuberculous Mycobacterial Infections (NTMI): Assessing the Role of Surgery and Trends in Macrolide Resistance

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Scholarly Report Title: Retrospective Observational Study of Pulmonary Non-Tuberculous Mycobacterial Infections: Assessing the Role of Surgery and Trends in Macrolide Resistance

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Abstract

Title: Retrospective Observational Study of Pulmonary Non-Tuberculous Mycobacterial Infections: Assessing the Role of Surgery and Trends in Macrolide Resistance

Purpose: Pulmonary non-tuberculous mycobacterial infections (NTMI) are persistent infections that are associated with significant health care utilization, morbidity and mortality. Current medical treatment for NTMI has limited efficacy, especially among macrolide resistant isolates. Although macrolide antibiotics are now recommended for prophylaxis among patients with chronic lung disease, there is limited surveillance of macrolide resistance among NTM isolates. For some patients, surgery may be an adjunct to medical treatment, but there is a paucity of controlled outcome data for surgery compared with medical therapy alone especially for the most common NTMI infection with *M. avium complex (MAC).* Here we perform a retrospective cohort study of MAC infection to assess the role of surgery and in addition assess trends in macrolide resistance amongst all NTM species cultured from patients receiving care in multi-institutional health care system in Boston.

Methods: Patients meeting American Thoracic Society (ATS) microbiologic criteria for the diagnosis of NTMI between 2001 and 2016 were identified through a retrospective electronic chart review and separated according to treatment received. We included only patients with radiologically focal MAC disease who received an adequate antimycobacterial regimen. We assessed the effect of surgery on 2-year all-cause mortality, microbiologic response, body mass index, pulmonary function, and radiographic disease through univariate and multivariate logistic regression. The yearly prevalence of macrolide resistance was calculated from positive non-tuberculous mycobacteria (NTM) cultures sent for drug susceptibility testing and analyzed for significant trends using a chi-squared trend test.

Results: Of 745 patients meeting microbiologic diagnostic criteria for NTMI, a total of 98 patients met the inclusion criteria and 16/98 (16%) of patients underwent surgical resection for NTMI treatment. Surgically treated and medically treated patients were similar in their baseline demographics, comorbidities, and FEV1. Although statistical power was limited, univariate analysis showed no statistically significant improvement in 2-year all-cause mortality (OR=0.87, 0.18-4.32), lack of microbiologic response (OR=0.49, 0.1-2.41), BMI outcomes (OR=0.35, 0.04-3.45), pulmonary function outcomes (OR=1.44, 0.19-11.1), radiographic outcomes (OR=0.88, 0.24-3.28) or composite outcome (OR=0.47, 0.12-1.79). Multivariate logistic regression for the effect of surgery on composite outcome indicated no statistically significant benefit to surgery (OR=0.45, 0.09-1.57). A total of 460 patients had

microbiologic samples sent for macrolide susceptibility testing between 2001 and 2016 with MAC as an increasing proportion of this sample (p<.001) and *M. abscessus* (MAB) decreasing as proportion of this sample over this time period (p<0.001). The rate of macrolide resistance significantly increased over that time period (p=.03) from 0% in 2001 to 14% (95% CI 7.5-20.8%) in 2016.

Conclusion: This is the first case-control study assessing the causal effect of surgery on outcome for patients with MAC pulmonary infection. As surgery for MAC disease is rare, sample size and power were limited, despite this surgery was measured to have a favorable albeit not statistically significant effect on all assessed outcomes except pulmonary function. We found a significant increase in the prevalence of macrolide resistance in NTM, though still rare, surveillance should be continued over time for this emerging issue.

Glossary of abbreviations

NTM: non-tuberculous mycobacteria

NTMI: non-tuberculous mycobacterial pulmonary infections

MAC: *Mycobacterium avium complex*

MAB: *Mycobacterium abscessus*

RPDR: Partners Research Patient Data Registry

Description of Scholarly Project

Mycobacterium Avium Complex (MAC) is a persistent pulmonary infection with current medical treatments having poor efficacy with low rates of clinical or microbiological response. For some patients, surgery has been proposed as an adjunct to medical treatment, but there are limited studies evaluating the benefit of surgery for patient outcomes. There have been limited investigations looking at optimal treatment for patients. Here we perform a case-control study of treatment outcome among patients with MAC pulmonary infection who received adjuvant surgical resection. Additionally, there are concerns for potentially increasing rates of resistance to widely used macrolide antibiotics, though rates of resistance are currently unknown. There is limited data on macrolide resistance among NTM and trends over time. Therefore, here we assess the rate of macrolide resistance testing and confirmed resistance among NTM culture positive patients and assess trends of this over time.

Student and Collaborator Contributions

This manuscript is being submitted as a first author contribution for fulfillment of my scholarly requirement. The concept for the project was initially suggested by Dr. Maha Farhat who predominately does work in *Mycobacteria tuberculosis* genomics, but as a practicing pulmonary critical care physician, she has also encountered patients with atypical mycobacterial infections where the question of surgical benefit in the care of these patients often arises. Dr. Farhat had a brief proposal outlining the case-control design with overview of important factors to control for, which I utilized develop as guide in drafting the IRB for our project. On approval of our IRB, we were given patient records in the form of semi-structured and unstructured .txt files for which we could develop extraction. As somebody without prior significant experience in programming, I utilized courses online to learn Python data science techniques in order to develop code for extraction of key variables that we acquired from the .txt files.

After completion of variable extraction, Dr. Farhat and I had weekly meetings in order to discuss the subtleties and variable coding and defining outcome variables to make sure that our study was as statistically rigorous as possible while still appropriately accounting for foreseeable confounders. With guidance, I was able complete the statistical analysis, produce figures and tables, and produce the initial draft of the manuscript which will be submitted to the *Journal of Clinical Infectious Disease*. Dr. Maha Farhat has edited the manuscript with multiple iterations between her and I. She has approved this draft for submission to HMS, but we are awaiting collaborators approval prior to submission.

Drs. Hurtado, Richards, and O'Donnell manage these patients with atypical mycobacterial infections in the outpatient setting so they were instrumental in helping us to ensure that we were appropriately accounted for the cofounder of antimycobacterial regimen per practice standards, in addition to consulting on the appropriateness of our outcome variable definitions given the data that was available to us. Rakesh is an MPH student who was part of the project as part of his practicum, for which he assisted with portions of the variable extraction process.

Manuscript- Main Text (Not Yet Published)

Background

Non-tuberculous mycobacterial species (NTM) are ubiquitous environmental organisms and are subdivided into two main categories: fast growers that include *M. abscessus* (MAB) *and M. Kansasii,* and slow growers that include *M. avium complex* (MAC) [1]. Patients who are immunocompromised (HIV, medically immunosuppressed) or have underlying structural lung disease (e.g. cystic fibrosis) are particularly at risk for NTM related pulmonary infections (NTMI). But NTMI can nevertheless affect patients without either of these predisposing factors [2]. Efforts to understand NTMI in immunocompetent individuals thus far have characterized at-risk patients as predominantly older women, with higher than average height and lower than average body mass index (BMI), and with higher rate of certain comorbidities, such as breast cancer [3].

NTMI are increasing in prevalence in the US and are associated with high rates of morbidity, mortality and health care cost [4–6]. Similar to *Mycobacterium tuberculosis*, these species have a high level of intrinsic drug resistance and medical therapy entails a complex multidrug regimen of 3-5 drugs given in combination. Clinical and microbiological response is often limited ranging between 8-41% [7–9] even when state of the art therapy is provided. As a result, for patients with anatomically appropriate disease, surgical resection has been proposed as sole or adjuvant therapy, despite the limited evidence base. Factors often weighed in deciding to pursue surgery as a treatment option include the failure of medical-management, co-morbidities that elevate the risk of thoracic surgery, and the anatomical extent of disease [10,11]. There has been one controlled study and several small case series describing outcomes of lung resection for NTMI yet there is a need for more controlled studies that examine other NTMI than MAB and compare both microbiologic response as well as hard outcomes like mortality between surgical and medical treatment [9,10].

Additionally, infection with macrolide resistant NTM is associated with poor treatment outcomes and an increased mortality rate [12,13]. Macrolides are recommended as part of multidrug antimycobacterial regimens in many NTM infections [4]. Macrolide monotherapy or regimens that consist of a macrolide and a quinolone have been associated the development of macrolide resistance [14]. More recently, it has been postulated that the use of macrolides for the treatment of other respiratory infections, or for the prophylaxis of chronic obstructive pulmonary disease beginning in 2011, and subsequently in bronchiectasis and cystic fibrosis (CF) exacerbations, may contribute to increased resistance [13,15]. Yet, there is limited data on macrolide resistance among NTM and trends over time. As a result, here we assess the rate of macrolide resistance testing and confirmed resistance among NTM culture positive patients and assess trends of this over time.

Aims

We hypothesize that surgical resection in patients with MAC disease, with anatomically focal disease, who have been treated with a multidrug antimycobacterial regiment will have superior microbiologic response and 2-year mortality. Here we perform a case-control study of treatment outcomes among patients with MAC pulmonary infection who received adjuvant surgical resection. Further, we hypothesize with the use of macrolide antibiotics as prophylaxis for common pulmonary conditions, there may be a trend for increasing resistance to macrolides amongst NTM isolates.

Methods

Data Extraction

The Partners Healthcare system is a multicenter health system with two large tertiary hospitals in its network and three community hospitals that act as referral centers for patients with NTMI. The Partners Research Patient Data Registry (RPDR) [16], a centralized electronic record based database designed for clinical research containing clinical data on 6.5 million patients who have received care through the Partners Healthcare system, was queried for ICD-9 (31.0/31.2) or ICD10 (A31.0/A31.2) diagnostic codes indicative of NTMI between the years

January 1st 2001- December 31st 2016. Clinical data for patients with at least one of the ICD codes above recorded during the study period was obtained and securely stored for data extraction. Clinical data was securely accessed per institutional protocol until a complete de-identified database of patient and relevant variables could be produced. The Partners Healthcare and Harvard Medical School institutional review boards for human subject's research approved the study protocol.

We queried the following clinical data elements: demographics, diagnostic billing codes, discharge summaries, operative reports, physician notes, medication reports, microbiology reports, pulmonary function reports, cardiac reports, radiologic reports, and BMI data. Clinical data consisted of semi-structured and unstructured reports. We developed Python 3 code to facilitate extraction of clinical data into a database and utilized the following open-source Python modules: Regular Expression, NumPy, and Pandas. Variable extraction code can be found in online repository https://github.com/farhat-lab/Non-tuberculous-Mycobacteria-Chart-Review .

For semi-structured data such as demographics, diagnostic billing codes, medication reports, microbiology reports, pulmonary function reports, BMI, and cardiac reports, regular expression-based pattern matching was used to identify and extract variables of interest. Figure 1 lists variables of interest that were extracted from semi-structured reports.

Figure 1- Variables extracted for registry from semi-structured data.
Demographics • Age at first diagnosis • Gender • Race • Date of death by social security registry or health system registry
Medications data • Pharmaceutical dispensing data for known NTM therapeutics
Billing diagnosis codes (ICD9/ICD10) • Pulmonary non-tuberculous mycobacteria • Gastroesophageal reflux disease • Chronic obstructive pulmonary disease • Breast cancer • Cystic fibrosis • Allergic bronchopulmonary aspergillosis • Rheumatoid arthritis • Previous tuberculosis • Smoking status

• HIV • Pectus chest deformity
Anthropomorphic data • BMI • Weight • Height
Pulmonary reports • Percent predicted Fev1, FVC, FEV1/FVC ratio
Cardiac reports • Mitral valve prolapse per echocardiogram reports
Microbiology • Mycobacterial smear, culture, and drug susceptibility testing with exclusion of tuberculous species

For data extraction from unstructured reports, both manual chart review and natural language processing (NLP) were utilized where feasible. For variables from operative reports, symptom data from physician notes and discharge summaries were manually reviewed and merged into our database. For radiologic variables, we developed NLP code that was able to identify radiologic findings of interest consistent with pulmonary mycobacterial infections and radiologist impression of these findings relative to prior imaging. An iterative approach was used to develop extraction code from unstructured reports until a random sampling of 25/25 (100%) consecutive encounters was accurately extracted. Specific variables extracted from unstructured reports are given in Figure 2. Further variable definitions and details on database development can be seen in appendix A.

Figure 2- Variables extracted for registry from unstructured data *Natural Language Extraction*	 *Manual Extraction*
Physician Notes and Discharge summaries • Symptoms (Cough, sputum production, dyspnea, weight loss, and fatigue)	Operative Reports • Surgical resection of lesion for known NTB infection

Radiology Reports
• Imaging modality (CT vs CXR)
• Radiologic lesions of consistent with mycobacterial infections
  ○ Cavitation
  ○ Bronchiectasis
  ○ Airspace Consolidation
  ○ Nodular opacity
• Location of pulmonary pathology (if focal, meaning isolated to 1 lobe)
• Radiologist impression specific lesions compared to prior imagining when available
	Physician notes
	• Symptoms
	  ○ Cough
	  ○ Dyspnea
	  ○ Weight loss
	  ○ Dyspepsia
	  ○ Hemoptysis
	  ○ Fatigue

Overall Patient Sample

We defined the overall study cohort based on the ATS microbiologic criteria for NTMI *i.e.* patients ≥2 cultures positive for NTM species, at least 1 positive acid-fast smear and 1 culture positive for NTM species or ≥1 bronchioalveolar wash culture positive for NTM species. Patients had to have both an ICD9/10 diagnostic code for NTMI (as above) and meet the ATS criteria to be included. As only a proportion of patients meeting ATS criteria are treated for NTMI in practice, we used this 'overall patient sample' to describe baseline patient characteristics and treatment rates.

NTMI Medical and Surgical Patient Sample

Inclusion Criteria

We restricted to patients (1) ≥18 years of age, (2) infected with a MAC species based on culture data as above or based on physician notes if the patient was referred for surgery and had no culture confirmation at the study heath system, (3) had focal mycobacterial disease on baseline imaging, and (4) received an 'adequate' medical treatment for MAC during their treatment course. In cases where patients had culture data with two or more species of NTM, those co-infected with MAB were excluded. Adequate MAC treatment was defined as a drug regimen containing at least the following drugs: (1) first line: clarithromycin or other macrolide, ethambutol, and rifampicin or other rifamycin, or (2) second line: first line with substitution of any of the drugs for clofazimine, bedaquline, or amikacin as these are often used as escalation therapy or in cases of drug intolerance. Focal disease on radiography was defined as evidence for lesions typical of NTMI (specifically bronchiectasis, nodular opacities, or consolidation) isolated to 1 lobe or any patient with a cavitary lesion regardless of number of lobes affected. We manually reviewed the patient record for patients who underwent surgery to ensure that the indication for resection was either due to NTMI refractory to medical therapy, adjunct therapy initial medical treatment, or as therapy for complications of NTMI, such as hemoptysis or symptomatic bronchiectasis.

Outcome Measures

Outcome measures were defined under 5 domains (1) microbiologic (2) radiologic (3) weight/nutritional status (4) pulmonary function and (5) mortality. For the microbiologic domain, microbiologic response was defined as sputum conversion from positive to negative within two years to treatment initiation or surgical intervention. Specifically, microbiological conversion was defined as either of the two following criteria (1) ≥2 negative cultures for patients with two or more follow-up cultures available without any recurrent positive culture or (2) one negative culture for patients with only one follow-up culture available within 2 years. For the radiologic domain, the main outcome measure was defined based on the radiologist's impression (improved or unchanged versus worsened) of a pulmonary lesion that is typical of NTM (bronchiectasis, cavitation, nodular opacity, or consolidation) on the last available imaging encounter with mention of these lesions occurring after treatment initiation or surgery. For nutritional status, outcome was defined as >5% decrease in body mass index (BMI) from baseline on first occurrence of follow-up BMI greater than 2 years after surgery or last record for an antimycobacterial. Worsening of pulmonary function was defined as a >12.5% decrease in FEV1 for non-obstructed patients and >25% decrease for obstructed patients based on the co-occurrence of an ICD billing for COPD baseline on first occurrence of follow-up PFTs greater than 2 years after surgery or last record for an antimycobacterial. Mortality was defined as 2-year all-cause mortality from the date of first diagnosis. Patients diagnosed after 1/1/2016 were excluded due to limited duration of follow up. A composite poor outcome variable was defined as mortality or the lack of microbiologic conversion within 2-years of treatment initiation.

Statistical Analysis

Univariate analysis was performed using the Fisher exact test for other binary variables and the Student's t-tests for continuous variables [17]. Multivariate logistic regression was used to control for potential confounders and assess the causal effect of surgery on MAC disease outcomes. We used a stepwise approach with both forward and backward elimination to build the final model. Any covariate with a P-value <0.20 was assessed for inclusion in the final

multivariate model. In addition, the variables of age, gender and surgical treatment were included in the model irrespective of their univariate P-value.

Macrolide Prevalence

Cultures positive for any NTM and/or tested for macrolide susceptibility were included in this portion of the analysis. Samples that underwent drug susceptibility testing for clarithromycin were coded resistant or susceptible based on report result, while intermediate samples were excluded. Replicate NTM samples within a calendar were excluded unless the patient had microbiologic conversion from susceptible to resistant, in which case only the resistant sample was included. The change in number of macrolide resistant NTM samples overtime was tested for significance using the Chi Square trend test (Cochran-Armitage test for trend).

Results

Overall Patient Population

From 2441 patients with a recorded ICD-9/10 billing code for NTMI between 2001-2016, a total of 752 met ATS microbiological criteria or were referred for surgical resection for NTMI related lung disease from an outside institution. Seven patients were further excluded due to age <18 years at the time of diagnosis. Among the 745 patients (Table 1) the mean age was 65 years (± 15), 67% were women, and 84% identified as White/Caucasian. The mean patient BMI was 23 (± 5) and the majority 68% were non-smokers. MAC was the predominant species of infection, present among 74% of the cohort. MAB was the second most common species and affected 15% of patients. The mean baseline percent predicted FEV1 was reduced at 67% and 54% of the patients had chronic obstructive pulmonary disease billing code recorded. Of the 745 patients, 24 patients underwent surgical resection of NTMI related lung disease and were similar to medically treated patients in their baseline characteristics, except for age at diagnosis and rates of coinfection with another NTM species which was significantly lower for the surgical group (Table 1).

Table 1. Baseline Patient Characteristicsc (Overall Population)					
		All Patients	Medical Patients	Surgical Patients	P-value
		n=745	n=721	n=24	
Demographics					
Age*		65 (sd=15)	65 (sd= 15)	58 (sd=12)	0.01
Female		498 (67%)	481 (67%)	17 (71%)	0.8
Non-White Race		117 (16%)	113 (16%)	4 (17%)	0.8
History of Smoking	n=509	164 (32%)	161 (32%)	3 (30%)	1.0
Comorbidities					
GERD		429 (58%)	414 (57%)	15 (63%)	0.8
ABPA		30 (4%)	29 (4%)	1 (4%)	1.0
COPD		399 (54%)	384 (53%)	15 (63%)	0.5
CF		73 (10%)	72 (10%)	1 (4%)	0.5
HIV		39 (5%)	37 (5%)	2 (8%)	0.4
RA		48 (6%)	47 (7%)	1 (4%)	1.0
Breast Cancer		58 (8%)	56 (8%)	2 (8%)	0.7
IBD		26 (4%)	25 (3%)	1 (4%)	0.6
Scoliosis		40 (5%)	38 (5%)	2 (8%)	0.4
Pectus Excavatum		1 (0.13%)	1 (0.14%)	0 (0%)	1.0
MVP		1 (0.13%)	1 (0.14%)	0(0%)	1.0
Disease Severity					
Weight Baseline	n=539	143 (sd=34)	143 (sd=35)	134 (sd=20)	0.2
BMI Baseline	n=532	23 (sd=5)	23 (sd=5)	22 (sd=3)	0.1
Baseline % Predicted FEV1	n=394	67 (sd=28)	67 (sd=28)	67 (sd=32)	1.0
Baseline % Predicted FEV1/FVC	n=391	84 (sd=18)	84 (sd=18)	86 (sd=13)	0.6
Baseline % Predicted FVC	n=390	79 (sd=26)	79 (sd=26)	76 (sd=37)	0.8
Species of Infection					
M. avium complex		554 (74%)	535 (74%)	19 (80%)	
M. Abscessus		111 (15%)	107 (15%)	4 (17%)	0.6
M. Kansasii		28 (4%)	27 (4%)	1 (4%)	
Other Species		52 (6%)	52 (7%)	0 (0%)	
Co-Infection		186 (25%)	185 (26%)	2 (8%)	0.05

GERD, Gastroesophageal reflux disease; ABPA, Allergic Bronchopulmonary Aspergillosis; COPD, Chronic Obrstuctive Pulmonary disease; CF, Cystic Fibrosis; HIV, Human Immunodeficiency virus; RA, Rheumatoid arthritis; IBD, Inflammatory Bowel Disease; MVP, Mitral Valve Prolapse; sd, standard deviation

*At time of diagnosis

Of the 24 NTMI patients treated with surgery, 23 were resected once. The remaining patient was resected twice with a 15-month interval. The majority 18/24 (75%) of patients had surgical resection of disease from one lobe and the remaining had a multi-lobar resection. The indication for surgery was listed as disease refractory to medical therapy in 13/24 (54.2%) patients and in 6/24 (25%) surgical resection was described as adjunct to medical therapy. For four patients, surgery was described as primary therapy for NTMI disease (n=3) or hemoptysis (n=1) and no medical therapy was given. The last patient did not tolerate medical therapy and subsequently underwent surgical resection as sole therapy. Baseline symptoms for surgical

patients are listed in order of frequency with cough (80%), sputum production (54%), hemoptysis (33%), weight loss (17%), fatigue (17%), and dyspnea (17%).

Radiographic distribution of lung disease

Chest imaging by computed tomography (CT) was performed at baseline for 713 of the 745 patients (Table 3). Corresponding radiology reports for 649/713 (91%) described one or more lesions typical of NTMI, namely bronchiectasis, cavitation, nodular opacities, and consolidation. Of these 649, 67% had disease that was reported as focal, involving no more than one lobe, or report of a cavitary lesion. CT reports were available for 23 of the 24 patients in the surgical group. Surgical patients with bronchiectasis were significantly ($p<0.03$) less likely to have diffuse rather than focal bronchiectasis compared to medical patients with bronchiectasis, with an odds ratio of 0.17 (0.06-0.4). Surgical patients overall were significantly ($p<.0001$) more likely to have cavitary lesions with an odds ratio of 6.15 (2.49-15.18).

Table 2. Distribution of lesions at baseline in patients with CT imaging

		Distribution of focal vs diffuse in medical patient with with a lesion found on CT	Distribution of focal vs diffuse in surgical patient with with a lesion found on CT	Odds ratio of surgical patient having diffuse lesion	% of medical patients with CT imaging who have lesion n=690	% of surgical patients with CT imaging who have lesion n=23	Odds ratio of surgical patient having a lesion (diffuse or focal)
Bronchiectasis	Diffuse	404 (82%)	10 (59%)	0.17 (0.06-0.4)	493 (71%)	17 (74%)	1.13 (0.44-2.91)
	Focal	89 (18%)	7 (41%)	P-value=0.03			P-value=1
Cavitary	Diffuse	112 (60%)	13 (81%)	2.9 (0.8 -10.53)	187 (27%)	16 (70%)	6.15 (2.49-15.18)
	Focal	75 (40%)	3 (19%)	P-value=0.2			P-value<.0001
Nodular opacity	Diffuse	44 (29%)	0 (0%)	n/a	153 (22%)	5 (9%)	0.75 (0.27-2.04)
	Focal	109 (71%)	5 (100%)	P-value=0.3			P-value=1
Consolidation	Diffuse	160 (60%)	2 (29%)	0.27 (0.05-1.43)	269 (39%)	7 (30%)	0.68 (0.28-1.69)
	Focal	109 (41%)	5 (71%)	P-value=0.1			P-value=0.5

Focal: defined if lesion only effecting 1 lobe

Diffuse: defined ≥2 lobes effected by lesion

NTMI Medical therapy

Because 554/745 (74%) patients were found to be infected with MAC we restricted our assessment of medical therapy to this subset. Only 154/554 or 28% of patients received multi-drug regimens that were considered to be effective against MAC (see methods). Of the 554, 400 (72%) did not receive any medical treatment. A chart review of 25 randomly chosen patients from the no treatment group confirmed that patients in this group were being monitored without therapy in the time period for which RPDR had clinical data available.

The effect of surgery on MAC disease outcomes

To assess the effect of surgical resection on outcome we nested a case-control study among the retrospective cohort of patients with NTMI. As surgical resection is only possible among patients with focal lung disease, we restricted to patients who received adequate medical treatment or surgery for focal MAC disease. A total of 98 patients met inclusion criteria, 16 of which underwent surgical resection. Figure 3 presents a flow chart for the identification of the surgical and medical groups respectively. The two groups were similar in baseline characteristics (Table 3). In univariate analysis there were no significant differences in defined outcome measures between surgical and medical cohorts (Table 4). Although the surgical group had a higher rate of microbiologic response with an odds ratio for lack of response of 0.49 (0.1-2.41), and lower rate of composite negative outcome compared to medical patients with an odds ratio of 0.47 (0.12-1.79) this was not statistically significant. We tested all covariates in Table 4 that had a univariate p-value <0.20 for inclusion in the multivariate model and only gender and age were retained. After adjustment in the multivariate model, the odds of a poor composite outcome related to surgery was unchanged at 0.45 (0.09-1.57).

Figure 3. Patient selection flow chart

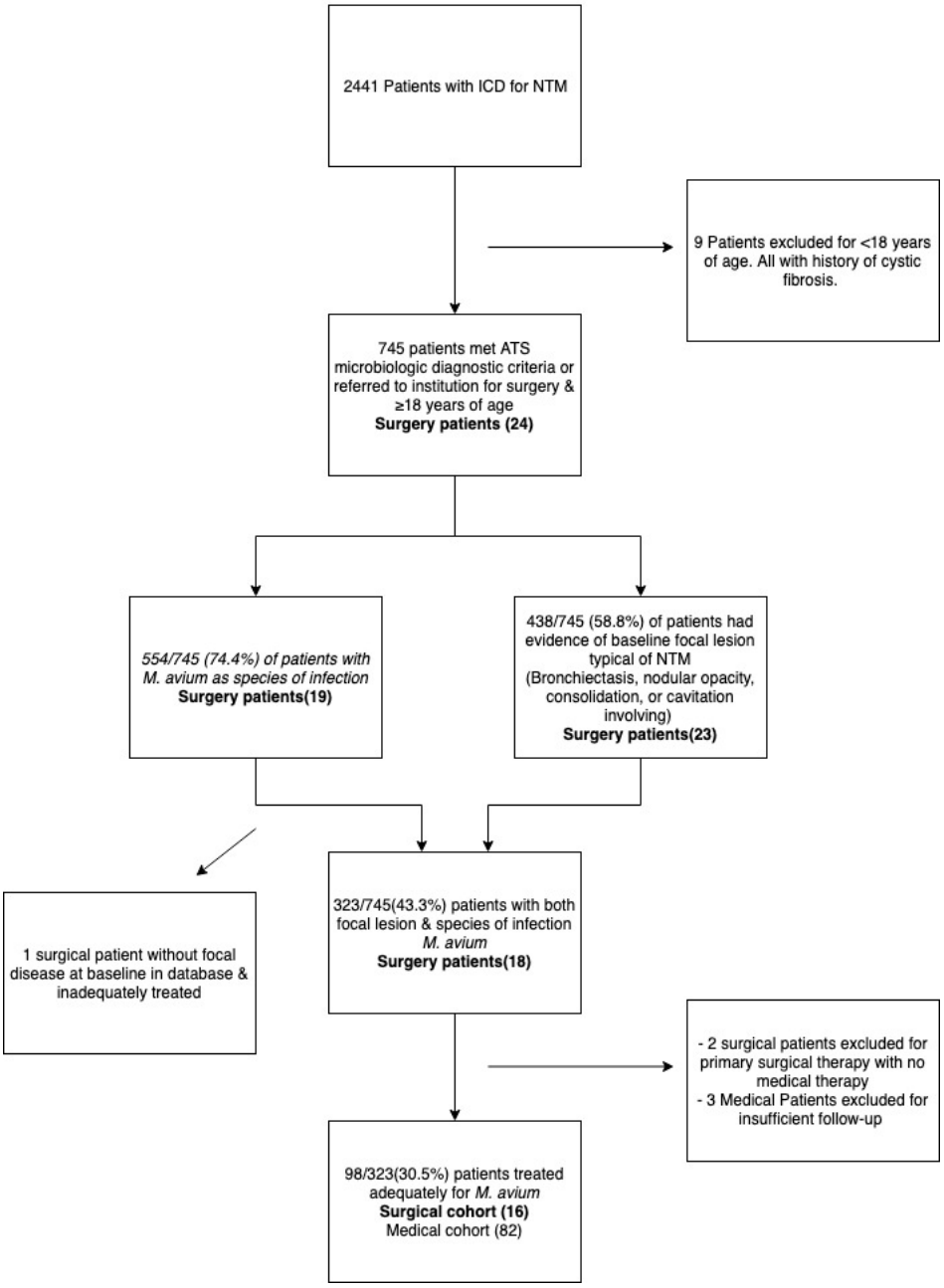


Table 3. Baseline characteristics of patients with MAC disease, focal lesion, and adequate medical treatment					
		Overall	Medical Cohort	Surgical Cohort	P-value
		n=98	n=82	n=16	
Demographics					
Age		60 (sd=12)	61 (sd=12)	55 (sd=13)	0.1
Female		62 (63%)	51 (62%)	11 (69%)	0.8
Non-White Race		15 (15%)	13 (16%)	2 (13%)	1.0
History of Smoking	n=62	20 (32%)	17 (32%)	3 (38%)	0.7
Comorbidities					
GERD		67 (68%)	56 (68%)	11 (69%)	0.8
ABPA		5 (5%)	4 (5%)	1 (6%)	1.0
COPD		61 (62%)	52 (63%)	9 (56%)	0.8
CF		8 (8%)	7 (9%)	1 (6%)	1.0
HIV		12 (12%)	11 (13%)	1 (6%)	0.7
RA		9 (9%)	9 (11%)	0 (0%)	0.3
Breast Cancer		7 (7%)	5 (6%)	2 (13%)	0.3
IBD		7 (7%)	6 (7%)	1 (6%)	1.0
Scoliosis		8 (8%)	6 (7%)	2 (13%)	0.6
Pectus Excavatum		0 (0%)	0 (0%)	0 (0%)	1.0
MVP		0 (0%)	0 (0%)	0 (0%)	1.0
Disease Severity					
Weight Baseline	n=55	141 (sd=30)	141 (sd=31)	136 (sd=22)	0.6
BMI Baseline	n=56	23 (sd=4)	23.2 (sd=5)	21.7 (sd=3)	0.2
Baseline % Predicted FEV1	n=58	64 (sd=29)	64 (sd=29)	70 (sd=35)	0.5
Baseline % Predicted FEV1/FVC	n=56	84 (sd=19)	84 (sd=20)	84 (sd=13)	0.9
Baseline % Predicted FVC	n=55	74 (sd=30)	75 (sd=30)	77 (sd=42)	0.8

GERD, Gastroesophageal reflux disease; ABPA, Allergic Bronchopulmonary Aspergillosis; COPD, Chronic Obrstuctive Pulmonary disease; CF, Cystic Fibrosis; HIV, Human Immunodeficiency virus; RA, Rheumatoid arthritis: ; IBD, Inflammatory Bowel Disease; MVP, Mitral Valve Prolapse; sd, standard deviation

*At time of diagnosis

Table 4. Surgical vs Medical cohort outcomes					
	All	Medical Cohort	Surgical Cohort	Odds ratio (95% CI)	P-value
Univariate Analysis	n= 98	n=83	n=16		
2-year all-cause mortality	14 (14%, n=97)	12 (15%)	2 (13%)	0.87 (0.18-4.32)	1.0
Lack of microbiologic response	21 (25%, n=83)	19 (27%, n=70)	2 (15%, n= 13)	0.49 (0.1-2.41)	0.5
Worsening BMI	7(22%, n=32)	6 (26%, n=23)	1 (11%, n=9)	0.35 (0.04-3.45)	0.6
Worsening PFTs	5 (21%, n=24)	3 (19%, n=16)	2 (25%, n=8)	1.44 (0.19-11.1)	1.0
Radiologic worseing	33(39%, n=82)	28 (39%, n=71)	4 (36%, n=11)	0.88 (0.24-3.28)	1.0
Composite Outcome: 2-year all cause mortality or lack of microbiologic response	30 (31%)	27 (33%)	3 (19%)	0.47 (0.12-1.79)	0.4
Multivariate Analysis*					
Surgery				0.45 (0.09-1.57)	0.2
Male				0.77 (0.30-1.91)	0.6
Age**				0.99 (0.96-1.03)	0.8

*Effect on composite composite outcome **At time of diagnosis

Prevalence of Macrolide Resistance

A total of 460 patients had microbiologic samples sent for macrolide susceptibility testing between 2001 and 2016. During this time period, MAC was an increasing proportion of this sample (P-value<0.001), with 0% 2001 to 75% in 2016, and MAB decreasing as proportion of this sample(P-value<0.001), with 100% in 2001 to 11% in 2016. The rate of macrolide resistance significantly increased (P-value=0.03) from 0% in 2001 to 14% (95% CI 8-21%) in 2016 within our sample. NTM isolates from 32 of 460 patients (7%) tested macrolide resistant at one or more time points. Of 166 patients who had ≥2 cultures sent for macrolide susceptibility testing, 12/166 (7%) had conversion from susceptible to resistant, of these 11/12 (92%) had documented exposure to macrolides in our database. Six of the 12 patients with resistance conversion were infected with MAC species, and one was infected with MAB. The remaining five patients had different NTM species cultured at different time points. Table 5 presents NTM macrolide susceptibility testing and resistance rates stratified by MAC and MAB.

Table 5. Trends in NTM macrolide resistance

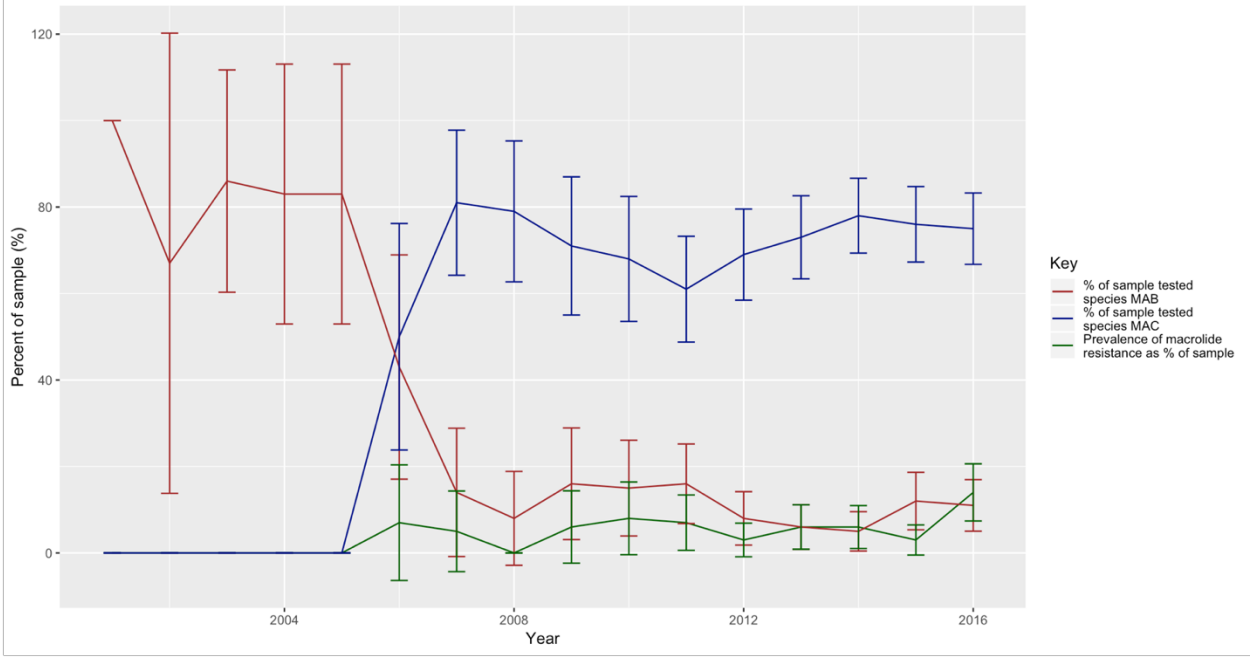
	All NTM (Tested/Positive, Resistant)	MAC (Tested/Positive, Resistant)	MAB (Tested/Positive, Resistant)
2001	4/68, 0 (0%)	0/54, 0 (0%)	4/7, 0 (0%)
2002	3/69, 0 (0%)	0/52, 0 (0%)	2/8, 0 (0%)
2003	7/81, 0 (0%)	0/59, 0 (0%)	6/7, 0 (0%)
2004	6/99, 0 (0%)	0/75, 0 (0%)	5/9, 0 (0%)
2005	6/116, 0 (0%)	0/91, 0 (0%)	5/10, 0 (0%)
2006	14/126, 1 (7%)	7/87, 1 (14%)	6/11, 0 (0%)
2007	21/123, 1 (5%)	17/74 0 (0%)	3/11, 0 (0%)
2008	24/122, 0 (0%)	19/84, 0 (0%)	2/7, 0 (0%)
2009	31/151, 2 (6%)	22/92, 0 (0%)	5/15, 2 (40%)
2010	40/163, 3 (8%)	27/106, 1 (4%)	6/26, 2 (33%)
2011	61/157, 4 (7%)	37/92, 1 (3%)	10/30, 2 (20%)
2012	74/172, 2 (3%)	51/113, 0 (0%)	6/17, 1 (17%)
2013	82/166, 5 (6%)	60/118, 2 (3%)	5/12, 3 (60%)
2014	88/169, 5 (6%)	69/123, 3 (4%)	4/18, 2 (50%)
2015	92/185, 3 (3%)	70/136, 1 (1%)	11/17, 1 (9%)
2016	106/181, 15 (14%)	79/141, 3 (4%)	12/12, 6 (50%)

In parentheses % of samples undergoing macrolide susceptility testing that are resistant

Figure 3 presents overall trends in the rates of NTM resistance to macrolides in addition to the proportion of yearly sample that is MAB or MAC. A high proportion of the resistant isolates were MAB (Table 5). As the recommendation for COPD prophylaxis with azithromycin is based on a randomized clinical trial published in 2011[15], we assessed if there was a significant

change in resistance rates since 2011. We observed no significant trend in resistance rates among MAC isolates since 2011 (rate between 1-4%, latter in 2016, P-value 0.6), but a significant trend overall among non-MAB NTM since 2011 (rate ranging between 1-10%, latter in 2016, P-value 0.02).

Figure 3. Prevalence of macrolide resistance in samples sent for macrolide susceptibility testing



-Sample defined as number of patients each year undergoing macrolide susceptibility testing
-Error bars represent 95% confidence interval of proportion

Discussion/Conclusion

We assembled a retrospective cohort of patients with NTMI receiving care at a multi-institutional tertiary hospital network using electronic health record data. The overall study population was similar to those previously described in the literature. The majority of affected patients being predominantly female, older, and with relatively low BMI compared to the general population [3,18] and the most common NTM species was MAC [19]. Seventy two percent of patients meeting ATS criteria for MAC disease did not receive any medical therapy, similar to other studies where observation rates for MAC disease were measured at 69.2% [20]. We observed 25% of patients with MAC disease to be co-infected with another NTM species. Although there are no prior studies reporting the frequency of co-infection for MAC patients our results are consistent with observations among MAB patients where co-infections occurred

among 13 to 55% [9,21]. The high rate of co-infection likely emphasizes the role of the patient environment and NTM reservoirs within that may potentiate pulmonary disease.

We attempted the first case-control study assessing the role of surgical lung resection in achieving sputum culture conversion or increasing 2-year survival among patients with MAC disease. Medical and surgical groups were similar in their baseline characteristics with the exception of the younger mean age at the time of NTMI diagnosis among the surgical group (58y vs. 65y), this is likely related to the lower assessed risk of surgery among younger individuals. Radiologically, surgical patients with bronchiectasis were significantly less likely to have diffuse bronchiectasis (≥2 lobes) and were significantly more likely to have cavitary lesions, both of which are more amenable to surgical resection[10]. Only 16/98 adult patients underwent surgical resection for focal MAC disease as an adjunct to medical therapy, and this significantly limited the power of our analysis to detecting an OR of 0.27 or lower. Despite the lack of statistical significance, the results are suggestive of improved outcomes after surgical resection as the measured odds were favorable across four assessed domains of outcome including radiological burden of disease, nutritional status, microbiological response and survival. The only measure that did not have a favorable odds was spirometric pulmonary function, however this is at least in part expected after surgical resection of lung tissue even if the tissue was diseased. Prior studies assessing the effect of surgery in patients with pulmonary disease related MAB, a fast-growing NTM, only assessed microbiological response or relapse[9]. The measured odds of unfavorable outcome was measured to be lower than what we have observed for MAC, measured at 0.35 (CI 0.10-1.09, Fisher P-value 0.07, Fisher test applied to data from Table 4 in ref [9] n=69) this suggests that surgery may have a more important role for MAB related disease than MAC, but due to the small sample size follow up studies or meta-analysis is required to confirm these findings. As expected, we observed a higher rate of 2-year microbiologic response after MAC medical treatment, 75% compared with 39-48% for patients with MAB disease [9].

Our study is limited by its retrospective design and the associated missing data for certain test results especially BMI measurements and spirometric pulmonary function. As testing is clinician driven, available data likely preferentially represents patients with higher disease severity. Our database is further limited by the lack of medication prescription details including number of refills and the duration of treatment. As a result we were not able to assess relapse after treatment. Despite this our study adds significantly to the prior very limited literature on this topic and is the first to assess the role of surgery in MAC disease and compare this to a carefully selected group of medically treated controls [10]. We also provide the first attempt to assess clinical outcomes beyond microbiological response including PFTs, BMI, and radiologic outcomes that are often used in clinical practice. Our retrospective design with a high rate of missing data for PFTs, BMI, and radiologic outcomes makes it difficult to conclude whether these outcome measures may be accurate measures of disease progression in patients with NTMI. Future studies, including the ongoing NTM patient registry efforts [22], should continue to correlate microbiologic response rates and mortality to these alternative outcomes of PFTs, BMI, and radiology in order to better assess clinical status for patients with NTMI. We also provide a de-identified patient database that can be included in future meta-analyses to better assesses these outcomes.

Macrolide resistance in NTM

The prevalence of NTM resistance to macrolide antibiotics appears to be increasing although the majority of resistant isolates are MAB, a species known to have intrinsic or inducible resistance. It is possible that the observed increase in resistance is related to improving diagnostic accuracy enabled by the recent availability of erm(41) gene testing [23]. However, even when we exclude MAB isolates, and assess trends since 2011 when macrolides became recommended for COPD exacerbation prophylaxis [17], we still observed a significant trend in NTM macrolide resistance over time. Additionally, in this analysis we found six patients with MAC conversion from macrolide susceptible to resistant. All of these patients were receiving macrolides among a multi-drug antimycobacterial regimen considered adequate as defined in our study. The phenomenon of MAC amplifying macrolide resistance has been well described in

the literature and is associated with poor outcomes [13]. There appears to be room for further improvement in antimycobacterial regimens to treat MAC NTMI. Overall, NTM macrolide resistance rates remain low and the observed trend is related predominantly to changing rates between 2015-2016 (Figure 3). Accordingly continued surveillance is recommended among clinical isolates especially in patients with previous exposure to macrolides.

Though underpowered, our case-control study showed no difference in outcomes in patients undergoing surgery compared to medical controls, suggesting no change to current practice should be made. The role of surgical resection in MAC NTMI remains undetermined and future studies will benefit utilization of large patient databases or in meta-analysis. Further, in assessing macrolide resistance in NTM we found increasing rates of resistance, but at a low level for which we advocate for ongoing surveillance.

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Appendix A-

Extraction Variable definitions
Study Period: 1/2001 to 12/31/2016.

Date of first diagnosis: This was coded on the first occurrence of an ICD or NTM.

Demographics

Age: Calculated from date of first appearance ICD for NTB using DOB. DOB not listed for deidentification. Missing ages coded as 0 due to missing 'date of first Dx' for ~60 patients.
Race: White, Black/African-American, Hispanic/Latino, American Indian, Asian, Native-Hawaiian
Date of death: Recorded if available from Records above

Outcome:
2-year all-cause mortality: Using the date of first diagnosis and the date of death we calculated the difference in these two dates. If a patient's time to mortality from the date of diagnosis was less than 2 years, the patient was coded for having the negative outcome of 2-year all-cause mortality.

Longitudinal Definitions
Baseline Reference Date: Baseline defined as first appearance of ICD for NTM infection. On table this is 'Date of first Dx'

Follow-up Date: This date is recorded in single column base on criteria below. This is used as the date to define follow-up outcomes

- Medical Treatment group (Patients that received a treatment defining medication). Last recorded date of a course of treatment defining medication.
    - Clarithromycin, Ethambutol, Rifampicin, Rifabutin, Clofazimine, Bedaqualine, Isoniazid, Amikacin
- Surgical Treatment group- Date defined by date of surgery for NTB. This date supersedes medical treatment date if both medical and surgical treatment were performed.
- If no treatment was given to a patient, this is defined as the last occurrence of NTM ICD.

Patient Characteristics and PMH
Weight Baseline: Weight that is nearest to baseline date occurring between 730 days to baseline reference date as above or 365 days after. Blank means no weights within the defined time range.
BMI Baseline: BMI that is nearest to baseline date occurring between 730 days to baseline reference date as above or 365 days after. Blank means no BMI within the defined time range.
Weight Follow-up: Earliest occurrence of weight occurring >730 days after follow-up date defined as above.

BMI Follow-up: Earliest occurrence of BMI occurring >730 days after follow-up date defined as above.

Smoking Status:

- Any former smoker or active smoker codes were coded = History of smoker
- Never smoker coded as is
- Blanks = no recorded smoking status for a given patient.

Past medical history(comorbidities) was obtained using any occurrence of ICD corresponding to a specific illness and coded as present unless otherwise noted below. Patients without occurrence of ICD were coded as not present.

Mitral Valve prolapse: Obtained based on echo reports. If presented coded present. If not present of echo this was coded if specifically commented on a report. Blanks mean no echo preformed.

Outcome:

We defined our BMI outcome as >5% decrease in BMI from baseline to follow-up BMI where this would be coded as a poor outcome.

Pulmonary Function Test

PFT Baseline: PFTs that is nearest to baseline date occurring between 730 days prior to baseline reference date as above or 365 days after. Blank means no weights within the defined time range.

PFT Follow-up: Earliest occurrence of PFTs occurring 2 years after defined follow-up date

Extracted PFT variables

- FEV1 % Predicted
- FVC % Predicted
- FEV/FVC % Predicted

Outcome:

Significant worsening (from baseline to follow-up as defined above) in % Predicted FEV1 defined a greater than 25% decrease for COPD patients and 12.5% decrease for non-obstructive patients.

Microbiologic Extraction

Positive Sputum Cultures: Number of positive sputum cultures for any non-tuberculous mycobacterial species

Positive BAL Cultures: Number of positive bronchial alveolar lavages cultures for any non-tuberculous mycobacterial species

 # number of Cxs sent: Total number of mycobacterial cultures sent of any type.

Total #of Smears: Total number of acid fast smears of any type that were sent.
1+, 2+, and 3 to 4+ counts: Positive smears per patient available.
Total Positive Smears: Total positive smears of any level of positivity included. (Sum of prior columns)

Date of Most Recent Pos Cx: Date
Negative Cultures since last positive: # of cultures that have been negative since the date reference in above.

Date of Most Recent Pos Smear: Reference Date

Date of First Pos Cx: Reference Date

Date of First Pos smear: Reference Date

Macrolide Susceptibility: For cultures with macrolide susceptibility testing, result was extracted per interpretation on result. Testing that was indeterminate was not used in this study.

Species of infection: Coded MAC, Kansasii, Abscessus, other(any species not previously listed). *If patient with multiple coinfected with 2 or more species, patients coded by heiarchy MAB>MAC>Kansasii>other species

Coinfection: Coded for any patient with 2 or more unique species listed.

Macrolide susceptibility conversion: In patients with 2 or more samples sent for macrolide susceptibility testing, if a patient went from a susceptible sample to a positive sample then coded and 'Conversion'.

Outcome:

Microbiologic Response:
For the microbiologic domain, microbiologic response was defined as sputum conversion from positive to negative within two years to treatment initiation or surgical intervention. Specifically microbiological conversion was defined as either of the two following criteria (1) ≥2 negative cultures for patients with two or more follow-up cultures available without any recurrent positive culture or (2) one negative culture for patients with only one follow-up culture available within 2 years.

<u>Medications</u>
For each patient we extracted every occurrence of an order for typical antimycobacterial medications from a list defined below. From this extraction we could create a list of

antimycobacterial medications that a patient had received at any point. This was the basis for defining patients with MAC that had received adequate treatment. Medication data only provided consistent data on the date of each medication was ordered without clear indication of duration. Ultimately, we did not control for multiple treatment regimens/prolong courses we did include this in our database. To define courses, the assumption was made that courses were no longer than 274 days or 9 months.

For a given medication, the first and last dates a medication was ordered were identified. If these were greater than 274 days apart, a patient was flagged for receiving at least 2 courses of that given medication. Using the date of first order as reference, we identified the last order within 274 days of that medication if any. Similarly, using the last order of a medication as reference, the earliest order occurring within 274 days prior of the last reference date. If there were any orders occurring between end date of first course and the start date of the most recent course, then the patient was flagged for having received at least 3 courses of that given medication.

Using the list below,
Treatment Defining Medications

1. Clarithromycin
2. Ethambutol
3. Rifampicin
4. Rifabutin
5. Clofazimine
6. Bedaqualine
7. Isoniazid
8. Amikacin

Other Extracted Medications

9. Azithromycin
10. Moxifloxacin
11. Levofloxacin
12. Kanamycin
13. Tobramycin neb or IV
14. Gentamycin
15. Linezolid
16. Cefoxitin
17. Ceftaroline/Avibactam-
18. Imipenem
19. meropenem
20. Tigecycline
21. Bactrim
22. Doxycycline

Adequate Treatment:
Taking patients that were infected with MAC, we defined adequate treatment for these patients as any if they had received at any time during their illness course if they had received a first line regimen containing Clarithromycin, Ethambutol, and Rifampicin/Rifabutin. With consensus of two infectious disease physicians who often treat patients with NTMI, we defined adequate treatment for patients who received Clofazimine, Bedaqualine, or Amikacin as substitute for first line drugs as they often do for escalation therapy or in cases of drug intolerance.

Treatment Attempt: Coded treatment attempt if partial therapy from regimen above.

Radiologic Data
Radiologic data was extracted from radiology reports by identifying key word occurrences in addition to localizing qualifiers to determine. Specifically, if a lesion was described to be occurring within **one or more lobes** in the lung, then this was coded as **diffuse**. If lesion only occurred in **one lobe** then this was coded as **focal** and the location of the affected lobe was captured. Date and radiology type were captured as well. CT abdomen reports were excluded as this may incorrectly only report on lesion of interest at the bases.

3 groups of baseline data were determined for each patient. **1.** First was baseline data obtained using CT with the lesion of interest present as this would be higher quality imaging. **2.** 2nd baseline data was reported for CXRs. **3.** And finally, the 3rd baseline data reported is for those reports in which the radiologist did not include information on whether the lesion of interest focal or diffuse. This final category is to ensure that occurrence of bronchiectasis is captured in cases where patients had no other

Blank data for patients signified that no finding for the lesion for the lesion interest was made on radiology reports.

The same process was repeated for follow-up radiology data extraction. Example of columns below for the example of bronchiectasis.

CT Baseline Date	CT Bronchiectasis Baseline	Location of Bronchiectasis on CT	CXR Baseline Date	CXR Bronchiectasis Baseline	Location of Bronchiectasis on CXR	Baseline Date-Bronchiectasis NOS	Bronchiectasis Baseline-NOS	Radiology Type-Bronchiectasis NOS(Baseline)

Lesions of interest include bronchiectasis, nodular opacities, cavitary lesions, and airspace opacities.

Outcome:
In addition to baseline and follow-up radiologic data, further extracted a radiologist define outcome measure. Taking the last chest imaging encounter available with radiologist commentary on change of a typical mycobacterial lesion (Bronchiectasis, Cavitary Lesion, Nodular opacity, or consolidation) using our natural language classifier to determine a

radiologist impression. Impressions were classified into worsened, unchanged, and improved with extraction of the specific lesion commented.

For our outcome defined it as any radiologist defined radiographic worsening of any lesion. Unchanged and improved lesions were coded together as a no worsening.

Symptom data

We had difficulty extracting symptom data through a natural language classifier given any given note could reference prior symptoms as well as current symptoms. We therefore limited our extraction to manual review of notes for surgical patients where clinicians commented on mycobacterial disease course. We extracted for cough, sputum, dyspepsia, dyspnea, weight loss, fatigue, and hemoptysis. If clinician commented that these symptoms were present baseline we coded appropriately as present and coded not present if a clinician explicitly said patient declined or there was not mention.