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Hospital-based antibiotic use in patients with *Mycobacterium avium* complex

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ABSTRACT Treatment guidelines exist for pulmonary *Mycobacterium avium* complex (MAC) infection, although studies suggest poor concordance in clinician practice. Using a national database including hospital encounters of laboratory-confirmed MAC patients, we sought to characterise US treatment practices.

We assessed patients in the Premier Healthcare Database from 2009 to 2013 with two or more MAC-positive cultures or one MAC-positive culture and the International Classification of Diseases (9th revision) code for pulmonary nontuberculous mycobacteria (PNTM). Treatment was characterised by patient-, provider- and facility-level factors; significant differences were assessed ($p<0.05$). Multilevel Poisson regression estimated adjusted relative risks (aRR) of receiving guidelines-based or macrolide resistance-promoting regimens.

Of 1326 MAC patients, 645 (49%) received treatment: 10% received guidelines-based treatment and 18% resistance-associated therapy. Patients were more likely to receive guidelines-based therapy if they had multiple hospital encounters (aRR 1.5), codes for PNTM (aRR 5.7) or tuberculosis (aRR 4.5) or radiological procedures (aRR 10.9); multiple hospital encounters (aRR 0.8) or a tuberculosis code (aRR 0.1) were less likely to be associated with receiving resistance-promoting regimens.

In hospital-based MAC patients, half received antibiotics active against MAC, a low proportion received therapy based on MAC guidelines and many received antibiotics that promote macrolide resistance. Improved implementation of guidelines-based treatment is needed to decrease use of regimens associated with macrolide resistance.

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Introduction

Nontuberculous mycobacteria (NTM) can cause pulmonary disease (PNTM) in susceptible individuals, including immunocompromised patients, those with structural lung disorders and older adults, particularly females [1, 2]. Although numerous NTM species are associated with disease, ~80% of all PNTM cases in the United States are due to *Mycobacterium avium* complex (MAC) [3]. Several population-based studies have found that PNTM-associated morbidity and mortality, particularly due to MAC, are increasing in the United States [1, 4–6]. Treatment remains difficult as drugs that are active against NTM are not always well tolerated by patients and therapy duration is long [2, 7, 8].

Current treatment guidelines from the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) for MAC-associated nonextensive nodular bronchiectatic lung disease in HIV-negative patients include a thrice-weekly regimen with a macrolide, rifampin and ethambutol; for patients with fibrocavitary or severe nodular/bronchiectatic MAC-associated lung disease, an additional aminoglycoside is recommended [2]. This combination both increases chances of successful culture conversion [9] and reduces the risk of developing macrolide resistance, which has been observed in relapse patients after treatment with macrolide monotherapy, and is associated with increased risk of treatment failure and death [2, 9, 10].

Clinicians often lack confidence in treatment effectiveness [11], and adherence to guidelines-based treatment regimens varies [12, 13]. Understanding treatment regimens prescribed to US MAC patients, and how practices vary by patient-, provider- and facility-level factors is critical for identifying gaps in the clinical management of this disease. Using a large national database of inpatient and outpatient US hospital-based encounters with patient-level health information, we characterised antibiotic treatment use in patients with pulmonary MAC.

Methods

A retrospective cohort study was conducted using Premier Healthcare Database, a large multicentre data repository with linked electronic medical records of inpatient and outpatient hospital system-based encounter-level data (online supplementary material). From 2009 to 2013, we identified all patients with two or more MAC-positive cultures from a pulmonary source, or one MAC-positive culture and an International Classification of Diseases (9th revision; ICD-9) code for pulmonary NTM (031.0). Patients with an ICD-9 code for disseminated NTM, HIV or laboratory-confirmed *M. tuberculosis* were excluded. Demographic, facility, clinical, antibiotic, radiology (chest computed tomography (CT) or radiography) and microbiological data were extracted for each patient (specific laboratory tests are described in the online supplementary material). Antibiotic data were based on charges for antibiotics prescribed during the encounter (treatment duration is unknown). Comorbidities (ever) were assessed using ICD-9 codes (online supplementary table S1). Radiological data included whether a procedure was performed. Co-infection was identified as anything pathogenic isolated from a respiratory sample in at least one encounter (commensal organisms were excluded [14]).

Antibiotics received at each encounter were categorised into previously described presumptive treatment regimens [9, 12], with some modifications (table 1). For example, if at an encounter a patient received a macrolide, ethambutol and rifamycin (±aminoglycoside), that encounter was counted under guidelines-based therapy, regardless of additional drugs received. Only drugs with potential activity against MAC were included; these were restricted to treatments received within 3 months after a MAC-positive culture. In addition, treatment regimens were characterised by selected patient-, provider- and facility-level factors, with significant differences assessed using Chi-squared or exact binomial tests ($p \leqslant 0.05$).

Modified Poisson regression models with a random effect for facility were used to identify factors associated with receiving any treatment, guideline-based therapy, or a macrolide resistance-associated regimen (table 1); adjusted relative risks (aRR) and associated 95% confidence intervals were estimated. Models included facility- (urban/rural, teaching status, bed size, region), encounter- (attending physician specialty, inpatient/outpatient status, co-infection status) and patient-level (age, sex, race, comorbidity) factors. All analyses were conducted using R 3.4.1 [16]. Significance was assessed at $p \leqslant 0.05$.

Results

Of 5 928 830 unique patients seen at 176 hospitals with microbiological data, 186 765 (3%) had an acid-fast bacilli culture performed and 7812 (0.1%) had one or more NTM-positive culture. MAC was isolated in 5531 (71%) of these. Patients with ICD-9 codes for disseminated NTM (n=116) or HIV (n=137) were excluded, as were cases with *M. tuberculosis* isolated (n=1318). Of the remaining patients, 1205 (30%) had two or more MAC-positives. An additional 121 patients with an ICD-9 code for pulmonary NTM (031.0) and one MAC-positive culture were identified, giving a total of 1326 cases in 116 facilities included in this analysis, with an incidence rate of 22 per 100 000 patients.

TABLE 1 Categories of treatment regimens prescribed for US hospital-based patients with laboratory-confirmed *Mycobacterium avium* complex (MAC)

Treatment regimens meeting ATS/IDSA guidelines [2]	Macrolide, ethambutol and rifamycin, optional parenteral aminoglycoside[#]
Treatment regimens that potentially promote macrolide resistance [15]	Macrolide monotherapy Macrolide plus fluoroquinolone Macrolide plus rifampin
Treatment regimens that are of unknown clinical significance [2]	Macrolide plus inhaled amikacin Macrolide plus linezolid Macrolide plus other agents[¶]
Treatment regimens that do not include macrolides	Ethambutol plus rifamycin Fluoroquinolone-based regimen Parenteral aminoglycoside-based regimen Linezolid-based regimen

Regimens focused on antimicrobials containing potentially active compounds targeting MAC. Drugs that had no efficacy against nontuberculous mycobacteria were not included in this analysis. ATS: American Thoracic Society; IDSA: Infectious Disease Society of America. [#]: aminoglycosides include amikacin and streptomycin; receiving these drugs qualified as "meeting guidelines" regardless of additional antibiotics received; [¶]: "alternative macrolide therapy"; see online supplementary table S2 for macrolide combinations.

MAC patients were older (66% aged ⩾65 years) and more likely to be female (58%) (table 2). Age-specific rates of pulmonary MAC ranged from 0.8 per 100 000 patients in those aged <18 years to 58 per 100 000 patients in patients aged ⩾75 years. The overall rate of disease in males was higher than females (incidence rate ratio (IRR) 1.2, 95% CI 1.1–1.3), driven by a significantly higher rate of disease among males aged 18–44 years than females (IRR 2.6, 95% CI 1.7–4.0). Overall, 606 (46%) MAC patients had multiple encounters (mean 2.2, range 1–21), half (53%) of which were outpatient visits. Among inpatient encounters, 80% were discharged home, 9% transferred to an alternative facility and 5% died or were transferred to a hospice (table 2). Only 8% of attending physicians were infectious disease specialists, 22% were internal medicine specialists and 31% were pulmonologists (table 2), not accounting for possible consultations. Overall, 71% of patients received a chest CT or radiograph, while only 47% of hospitalisations included this procedure. Facilities with MAC cases were primarily in the in the South (37%) and Midwest (30%), similar to the distribution of facilities in Premier. The majority (88%) were at urban facilities, and most encounters occurred in midsized facilities (52%) and in nonteaching hospitals (61%) (table 2).

Antimicrobial use in MAC patients

Of MAC cases, 49% (n=645) were treated with an antibiotic active against NTM. Among these, only 10% of patients received ATS/IDSA guidelines-based treatment, 18% a regimen associated with increased risk for developing macrolide resistance and 6% a macrolide-based treatment of unknown clinical benefit; 20% of patients received a nonmacrolide regimen (table 3). Among patients with multiple visits (n=606), 226 (37%) were treated during their first encounter, 7% receiving guidelines-based therapy and 15% resistance-associated regimens (9% received macrolide monotherapy) (table 3). A significantly lower proportion of patients received any treatment during their second encounter compared with the first (27% *versus* 41%, p<0.001). Of those treated at their subsequent encounter, a similar proportion (6%, p=0.5) received guidelines-based therapy, but significantly fewer (6%, p<0.001) received resistance-associated treatment (3% macrolide monotherapy). Among those treated, MAC cases with a PNTM ICD-9 code (n=272, 21%) were significantly more likely to receive guidelines-based therapy (38% *versus* 12%, p<0.001) or an alternative macrolide therapy (15% *versus* 9%, p=0.02) at their encounter than those without the code, and significantly less likely to receive a resistance-associated treatment (19% *versus* 32%, p<0.001) or a nonmacrolide therapy (28% *versus* 45%, p<0.001).

Treatment varied slightly by facility- and encounter-level factors. The largest hospitals (⩾500 beds) prescribed significantly fewer resistance-associated therapies (21%) than midsized (33%, p<0.001) and small (36%, p=0.003) hospitals (table 4). A higher proportion of encounters at facilities in the South and West received guidelines-based therapy (24% for both) than those in the Midwest and Northeast (11% and 13% respectively, p<0.05), and received a lower proportion of resistance-associated therapies than

TABLE 2 Patient-, hospital encounter- and facility-level characteristics of a cohort of US hospital-based laboratory-confirmed *Mycobacterium avium* complex (MAC) cases

MAC cases	1326
Sex	
Male	552 (42)
Female	774 (58)
Age years	
<65	457 (34)
⩾65	883 (66)
Ethnicity	
White	1023 (77)
Black	142 (11)
Hispanic	16 (1)
Other	145 (11)
Concomitant pathogen	
Yes	443 (33)
No	883 (67)
Hospital encounters	2862
Discharge status	
Home	2295 (80)
Death/hospice	139 (5)
Transfer	264 (9)
Other/unknown	164 (6)
Specialty of attending physician	
Infectious disease	228 (8)
Internal medicine	620 (22)
Pulmonology	882 (31)
Hospitalists	337 (12)
Other	795 (28)
Patient status	
Inpatient	1344 (47)
Outpatient	1518 (53)
Radiology (chest CT/radiograph)	
Yes	1338 (47)
No	1524 (53)
Facilities	116
Size (number of beds)	
<200	32 (28)
200–499	60 (52)
⩾500	24 (21)
Teaching status	
Yes	45 (39)
No	71 (61)
Setting	
Rural	14 (12)
Urban	102 (88)
Region	
Midwest	35 (30)
Northeast	22 (19)
South	43 (37)
West	16 (14)

Data are presented as n or n (%). CT: computed tomography.

encounters in the Northeast (South 24%, West 22%, Northeast 42%; p<0.001). Northeastern hospitals were more likely to prescribe resistance-associated therapies than any other region (table 4). Finally, hospitalists were slightly less likely than internal medicine specialists to prescribe guidelines-based therapy; there were no other significant differences in prescribing of any treatment (table 4).

Concomitant pathogens

Overall, 539 (41%) MAC cases had one or more concomitant respiratory pathogens. Of these, the most commonly identified pathogens included *Pseudomonas* spp. (36%), *Aspergillus* spp. (27%) and

TABLE 3 *Mycobacterium avium* complex patients and hospital encounters prescribed regimens active against nontuberculous mycobacteria

	Encounters where treatment was received	People who received treatment
Subjects	2862	1326
Macrolide, ethambutol, rifamycin (optional aminoglycoside)[#]	152 (5)	129 (10)
Macrolide monotherapy[¶]	146 (5)	143 (11)
Macrolide, quinolone[¶]	87 (3)	84 (6)
Macrolide, rifamycin[¶]	13 (0)	12 (1)
Macrolide, amikacin[+]	1 (0)	1 (0)
Macrolide, linezolid[+]	8 (0)	8 (1)
Macrolide, other[+]	84 (3)	72 (5)
Ethambutol, rifamycin[§]	21 (1)	21 (2)
Quinolone-based[§]	306 (11)	265 (20)
Aminoglycoside-based[§]	5 (0)	4 (0)
Linezolid-based[§]	15 (1)	13 (1)
No treatment received	2024 (71)	681 (51)

Data are presented as n or n (%). [#]: treatment regimens meeting American Thoracic Society/Infectious Disease Society of America guidelines; [¶]: treatment regimens that potentially promote macrolide resistance; [+]: treatment regiments that are of unknown clinical significance; [§]: treatment regimens that do not include macrolides.

Staphylococcus aureus (17%) (online supplementary table S3). Treatment differed slightly at encounters where a concomitant pathogen was identified. While those with a co-infection were no less likely to receive treatment overall than those without (28% *versus* 31%, p=0.1), those without a co-infection were more likely to receive a resistance associated regimen (10% *versus* 8%, p=0.05), particularly macrolide monotherapy (7% *versus* 4%, p=0.005). There were no other differences in treatment in these two groups.

TABLE 4 Number and proportion of treatment regimens prescribed for a cohort of US hospital-based laboratory-confirmed *Mycobacterium avium* complex patients, by provider- and facility-level factors, among those encounters receiving treatment

	Subjects	Guidelines based	Resistance associated	Other
Size of facility (number of beds)				
<200	118	18 (15)	42 (36)	58 (49)
200–499	434	74 (17)	144 (33)	216 (50)
⩾500	286	60 (21)	60 (21)[#,¶]	166 (58)[¶]
Teaching status				
Yes	480	87 (18)	149 (31)	244 (51)
No	358	65 (18)	97 (27)	196 (55)
Setting of facility				
Rural	44	10 (23)	8 (18)	26 (59)
Urban	794	142 (18)	238 (30)	414 (52)
Region of facility				
Midwest	185	20 (11)	53 (29)	112 (61)
Northeast	224	30 (13)	94 (42)[#]	100 (45)[#]
South	295	70 (24)[#,¶]	70 (24)[¶]	155 (53)
West	134	32 (24)[#,¶]	26 (22)[¶]	73 (54)
Specialty of attending physician				
Internal medicine	326	71 (22)	93 (29)	162 (50)
Pulmonology	78	15 (19)	19 (24)	44 (56)
Hospitalists	208	29 (14)[#]	70 (34)	109 (52)
Other	226	37 (16)	64 (28)	125 (55)

Data are presented as n or n (%). Significance p⩽0.05. [#]: significantly different from category 1; [¶]: significantly different from category 2.

Comorbidities

Of MAC cases, 52% (n=687) had a comorbidity reported at any time (online supplementary table S1). Of those with bronchiectasis (n=215, 16% of all patients), treatment was received at 112 encounters; no significant differences in treatment were identified between those with and without bronchiectasis. Among chronic obstructive pulmonary disease (COPD) patients (n=427, 32%), treatment was received at 420 encounters; patients with COPD more frequently received guidelines-based therapy (21% *versus* 15%, p=0.04) and less frequently received resistance-associated therapy (26% *versus* 33%, p=0.05) than those without COPD. Finally, there were 54 (4%) patients with an ICD-9 code for tuberculosis (TB) not laboratory-confirmed at any point during our study period. Treatment was received at 78 encounters. Patients with this code were significantly more likely to receive guidelines-based therapy (45% *versus* 15%, p<0.001) and significantly less likely to receive resistance-associated treatment (3% *versus* 32%, p<0.001) than those without this code (table 5).

There were 85 encounters (from 80 patients) where the recommended TB regimen of rifampin, isoniazid, pyrazinamide and ethambutol (RIPE) was received; most of these encounters (n=74, 87%) were the patient's first hospital visit. Of those with the TB ICD-9 code, 54% (n=38) received RIPE compared to only 3% (n=42) without the ICD-9 code.

Risk factor analysis for treatment type

Several significant predictors of receiving treatment were identified (table 6). Factors that increased the likelihood of receiving any treatment included having an ICD-9 code for PNTM (aRR 1.2, 95% CI 1.0–1.5) or radiography (aRR 10.5, 95% CI 6.6–16.8). Factors that increased the likelihood of receiving guidelines-based therapy included having multiple hospital encounters (aRR 1.5, 95% CI 1.0–2.2), an ICD-9 code for PNTM (aRR 5.9, 95% CI 3.9–8.8) or TB (aRR 4.5, 95% CI 2.8–7.2), or radiography (aRR 10.4, 95% CI 3.6–30.0). Significant predictors of receiving a potentially macrolide resistance-associated regimen included having had radiography (aRR 16.8, 95% CI 5.3–53.8). Patients were less likely to receive a resistance-associated regimen if they had multiple hospital encounters (aRR 0.8, 95% CI 0.6–1.0) or a TB ICD-9 code (aRR 0.1, 95% CI 0.03–0.4) (table 6). When evaluating timing of treatment among those ever treated, a higher proportion of MAC cases received resistance-associated (78%) than guidelines-based (57%) therapy at their first hospital encounter (p<0.001), and received guidelines-based (43%) more than resistance-associated (22%) therapy at subsequent encounters (p<0.001).

Discussion

Using a national database of US hospital-based patient encounters, we characterised treatment practices in patients with laboratory-confirmed MAC from 2009 to 2013. Additionally, we identified factors associated with receiving guidelines-based therapy, and with macrolide resistance-associated regimens. While half of MAC patients were treated with an antibiotic active against NTM, only 10% received an ATS/IDSA guidelines-based regimen. This is similar to previously reported studies from the US, Europe, and Japan [12, 17]. Further, nearly 20% of MAC cases received a regimen associated with an increased risk of developing macrolide resistance, which is linked to treatment failure and adverse outcomes [9, 12, 16]. However, these rates varied by comorbidity and encounter-/provider-level characteristics. Because guidelines-based treatment is believed to be critical for successful outcomes among MAC patients, understanding factors driving differences in regimen prescription practises is crucial for improving clinical practise and reducing excess morbidity.

Among MAC cases who had a PNTM ICD-9 code, 38% received an ATS/IDSA-based regimen, which is three-fold higher than among those without a PNTM ICD-9 code. This suggests greater clinician awareness of ATS/IDSA guidelines among those who regularly use this code. Still, only 21% of all MAC cases identified here had an ICD-9 code for PNTM, which is similar to estimates of PNTM code usage when evaluated among ATS-confirmed NTM cases from prior studies [18, 19]. While it is recognised that the PNTM ICD-9 has poor sensitivity for identifying confirmed NTM cases, the difference in the frequency of receiving guidelines-based therapy identified here based on the presence of this code indicates that many MAC cases who did not have the PNTM code may have in fact benefited from receiving guidelines-based therapy.

The high rate of patients receiving macrolide resistance-associated regimens reported here and elsewhere [12, 17] remains concerning. We found that for patients with multiple encounters, those treated at a subsequent encounter rather than their initial visit had more than a two-fold lower rate of receiving such a regimen compared to those treated at their first encounter. It is possible that because culture-based testing for MAC can take 8–21 days [2, 14], diagnosis and therefore treatment decisions may be delayed. Although it is reassuring to see fewer patients receiving resistance-associated regimens at subsequent visits, expert opinion suggests that treatment success is greatest when the proper regimen is prescribed at the first

TABLE 5 Hospital encounters where treatment regimen was prescribed by comorbidity for laboratory-confirmed *Mycobacterium avium* complex cases, among encounters where treatment was received

	Pulmonary NTM	Alveolitis/ pneumonitis	Bronchiectasis	Coccidioidomycosis	COPD	CF	Histoplasmosis	IPF	Neoplasm	Non-HIV immunodeficiency	Sarcoidosis	TB
Subjects	189	2	112	1	420	9	3	2	44	15	9	78
Macrolide, ethambutol, rifamycin (optional aminoglycoside)[#]	72 (38)	0 (0)	21 (19)	0 (0)	88 (21)	3 (33)	1 (33)	0 (0)	7 (16)	5 (33)	2 (22)	35 (45)
Macrolide monotherapy[¶]	16 (8)	1 (50)	22 (20)	0 (0)	66 (16)	0 (0)	0 (0)	0 (0)	12 (27)	3 (20)	0 (0)	0 (0)
Macrolide, quinolone[¶]	14 (7)	0 (0)	12 (11)	0 (0)	38 (9)	1 (11)	0 (0)	0 (0)	4 (9)	0 (0)	2 (22)	1 (1)
Macrolide, rifamycin[¶]	6 (3)	1 (50)	3 (3)	0 (0)	6 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Macrolide, amikacin[+]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Macrolide, linezolid[+]	1 (1)	0 (0)	0 (0)	0 (0)	7 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Macrolide, other[+]	28 (15)	0 (0)	8 (7)	0 (0)	37 (9)	1 (11)	0 (0)	0 (0)	2 (5)	0 (0)	1 (11)	14 (18)
Ethambutol, rifamycin[§]	4 (2)	0 (0)	1 (1)	0 (0)	11 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (12)
Quinolone-based[§]	42 (22)	0 (0)	43 (38)	1 (100)	159 (38)	2 (22)	1 (33)	2 (100)	16 (36)	5 (33)	4 (44)	1 (33)
Aminoglycoside-based[§]	3 (2)	0 (0)	0 (0)	0 (0)	1 (0)	2 (22)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Linezolid-based[§]	3 (2)	0 (0)	2 (2)	0 (0)	6 (1)	0 (0)	1 (33)	0 (0)	2 (5)	2 (13)	0 (0)	0 (0)

Data are presented as n or n (%). NTM: nontuberculous mycobacteria; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis; IPF: idiopathic pulmonary fibrosis; TB: tuberculosis. [#]: treatment regimens meeting American Thoracic Society/Infectious Disease Society of America guidelines; [¶]: treatment regimens that potentially promote macrolide resistance; [+]: treatment regiments that are of unknown clinical significance; [§]: treatment regimens that do not include macrolides.

TABLE 6 Multilevel, multivariable modified Poisson regression assessing predictors of receiving guidelines-based therapy or macrolide resistance-associated therapy among laboratory-confirmed *Mycobacterium avium* complex cases

	Any regimen	Guidelines-based therapy	Resistance-associated therapy
Multiple hospital encounters	1.1 (0.9–1.2)	1.5 (1.0–2.2)*	0.8 (0.6–1.0)*
Pulmonary NTM ICD-9 code (no/yes)	1.2 (1.0–1.5)*	5.9 (3.9–8.8)#	0.7 (0.5–1.1)
COPD ICD-9 code (no/yes)	1.1 (0.9–1.3)	1.1 (0.7–1.6)	1.0 (0.7–1.3)
TB ICD-9 code (no/yes)	1.2 (0.9–1.6)	4.5 (2.8–7.2)#	0.1 (0.0–0.4)#
Concomitant pathogen isolated (no/yes)	1.0 (0.8–1.2)	0.9 (0.6–1.4)	0.8 (0.6–1.1)
Radiology conducted (no/yes)	10.5 (6.6–16.8)#	10.4 (3.6–30.0)#	16.8 (5.3–53.8)#

Data are presented as adjusted relative risk (95% CI). Random effect for facility was included in regression. Additional covariates were controlled for at the facility-level (setting, teaching status, number of beds, location), encounter-level (admission source, specialty of attending physician, inpatient status), and patient-level (age, sex, race). NTM: nontuberculous mycobacteria; ICD-9: International Classification of Diseases (9th revision); COPD: chronic obstructive pulmonary disease; TB: tuberculosis. *: $p \leqslant 0.05$, #: $p \leqslant 0.005$.

treatment attempt, indicating the importance of correctly treating MAC from the earliest point possible [16, 20, 21]. Receiving regimens that are not fully compliant with guidelines but still contain a macrolide and at least one other active agent might be due to tolerability issues associated with many NTM drugs [21–24] or the high cost of particular regimens [25]. This dataset does not allow us to determine whether these regimens were selected as the primary, intended treatment choice, or whether other recommended therapies were avoided due to adverse events or pre-existing conditions. Regardless of the intent, treatment with these regimens increase the patient's risk for macrolide resistance, which greatly reduces effective treatment options and results in poorer outcomes [9].

As PNTM patients are usually admitted for an alternative primary diagnosis, it is likely that many of the MAC cases identified here presented initially with concerns that warranted testing for respiratory pathogens such as suspicion of community-acquired pneumonia, rather than NTM specifically, which would play a role in empiric therapy choices. In fact, 33% of patients had a concomitant respiratory pathogen isolated. This finding is not unexpected, as NTM infections are associated with damaged or atypical pulmonary anatomy, predisposing patients to infection by opportunistic pathogens and complicating NTM treatment [26–28]. We did observe minor differences in treatment, with a significantly lower proportion of those without a concomitant pathogen receiving a resistance-associated regimen; however, this difference was not significant when controlling for other patient- and facility-level factors. This finding is similar to what was reported by Fujita *et al.* [28], who found that 65% of MAC patients with a co-infection were treated with a guidelines-based regimen for MAC, but that this proportion did not differ from those MAC patients without co-infection. Most co-infected patients who were treated received a non-macrolide, fluoroquinolone-containing regimen, except for those with *Streptococcus pneumoniae* who most frequently received macrolide monotherapy, which is the ATS/IDSA recommendation for treatment of outpatient pneumonia [29]. Still, it is important to recognise that given co-infection with pulmonary MAC, this regimen places these patients at increased risk for developing macrolide resistance.

Similarly, patients with certain comorbidities or genetic diseases such as cystic fibrosis (CF) have a known increased risk for NTM [30–32], which may also impact treatment choices. Thus, we observed differences in treatment depending on which comorbidities were present. As expected due to its association with NTM, COPD patients were more likely to receive guidelines-based therapy than patients without COPD. Further, several comorbidities require chronic use of medications such as immunosuppressants that can increase the likelihood of acquiring NTM or can affect treatment success. Corticosteroids for the treatment of conditions such as CF, COPD, and rheumatoid arthritis have been demonstrated to increase the risk for NTM, although the exact biological mechanism for this has not been determined [33–35]. Anti-tumor necrosis factor and other small biologicals interrupt the signalling pathway that activates host response to intracellular pathogens such as NTM [36–39]. Still, this should only serve to increase clinical suspicion for NTM given symptoms and should be considered when prescribing antibiotic treatments.

This analysis is subject to several limitations. Because dates were available only for the month of service, we were unable to assess treatment duration, an important aspect of guideline adherence which impacts

patient outcomes, nor could we determine whether treatment or culture results occurred first when both were within the same month. Furthermore, we were unable to rule out short-course macrolide regimens prescribed for reasons other than MAC. In addition, we lacked data on medication allergies or associated adverse reactions, which can affect treatment adherence and/or medications prescribed. Additionally, because this dataset only captures visits to participating providers, prescriptions filled at outpatient locations such as commercial retail pharmacies will have been missed. This limitation could bias our results toward individuals with more severe disease and/or those requiring more frequent hospital-based encounters, as well as excluding treatment changes after discharge where an appropriate revision in therapy could be made, especially as it is likely that clinicians are often unaware of the presence of MAC at the time of initial treatment. Treatment by attending physician specialty was biased toward those who had been treated in hospital, especially among pulmonologists, as most (83%) pulmonology-attended encounters were outpatient and much of their potential treatment prescriptions were likely missed. Finally, drug susceptibility data were unavailable for most MAC patients in this dataset. When macrolide resistance is present, it is recommended that patients receive ethambutol and rifamycin in addition to a parenteral agent [2]. While we were unable to determine the resistance profile of these infections, we found a very low proportion of hospital encounters where this was prescribed (<2%). Despite these limitations, this analysis still represents the largest description of treatment practises among a nationally distributed cohort of US MAC patients with clinical and microbiological data available, providing insight into current gaps and challenges in the diagnosis and treatment of pulmonary MAC.

Conclusions

At hospital encounters, patients positive for MAC were less likely to receive antibiotics consistent with MAC guidelines than treatment likely to promote macrolide resistance, especially at first treatment. It is believed that receiving effective therapy maximises the success of treatment and improves patient outcomes [11], and when macrolide resistance is present, clinical outcomes for these patients are poor, with many succumbing to respiratory failure before they are able to clear the pathogen [9, 40]. Therefore, it is important to use regimens that do not promote macrolide resistance in the presence of a pulmonary MAC infection whenever possible. Increased efforts are needed for physician education to ensure understanding and implementation of the ATS/IDSA guidelines for MAC treatment.

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