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Rate of All–Cause Hospitalization at Year 2 Between Treatment Groups Following Diagnosis of Nontuberculous Mycobacterial Lung Disease in the US

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BACKGROUND

- Nontuberculous mycobacterial lung disease (NTMLD) is increasingly common, with evidence from the past 3 decades indicating increasing prevalence in the United States and worldwide[1,2]
- NTMLD is a chronically progressive and potentially debilitating disease that can lead to a decline in lung function,[3] impaired quality of life,[4] and increased risk of mortality[5]
- *Mycobacterium avium* complex (MAC) is the most commonly isolated pathogen in NTMLD in the United States[2]
  - The ATS/IDSA clinical guidelines (2007) recommend initial treatment of NTMLD due to MAC with a multidrug regimen consisting of a macrolide, rifamycin, and ethambutol that should be continued until culture conversion is achieved and sustained for 12 months[6]
  - NTMLD caused by *Mycobacterium abscessus* infection is more difficult to treat due to antibiotic resistance[6]
- Given the chronic and slowly progressive nature of the disease, along with the need for prolonged treatment, patients with NTMLD experience multiple exacerbations which often require recurring hospitalization[7,8]
  - A recent retrospective analysis utilizing data from the Healthcare Cost and Utilization Project reported over 20,000 hospital discharges for NTMLD in the United States from 2001 through 2012[9]
- Despite the growing prevalence of NTMLD, data characterizing the associated healthcare resource burden at the national level are limited

OBJECTIVE

- To compare hospitalization rates between 3 treatment groups—Standard of care (SOC; ie, guidelines-consistent therapy), Other (other antibiotics), and Untreated—in patients with NTMLD in a US national managed care claims database

METHODS

- A national managed care insurance database was searched for physician claims for NTMLD (International Classification of Diseases, Ninth Revision [ICD-9] code 031.0 or Tenth Revision [ICD-10] code A31.0) on ≥2 separate occasions ≥30 days apart between 2007 and 2016
- A patient cohort was selected by including those who were insured continuously over 36 months, beginning 12 months prior to the first diagnostic claim of NTMLD and continuing 24 months after the claim
- Patients were classified into 3 groups based on the type of treatment they received in year 1 after the first NTMLD diagnosis (**Table 1**)
  - *Treatment group* was defined by first identifying SOC therapy, then identifying other non-SOC drugs, and then identifying no treatment
  - *Drug use* was defined by ≥30 days of continuous drug supply during the first year after NTMLD diagnosis. *No treatment* was defined as drug use with <30 days of continuous supply
- Patient comorbidities were identified using ICD-9 or ICD-10 codes, and use of select immunosuppressive therapies were identified through pharmacy dispensing claims (**Table 2**)
- NTMLD-related resource use was determined by isolating claims that contained a code for NTMLD. NTMLD-related values are likely to be underestimated due to an overall tendency of undertesting and undercoding for NTMLD in clinical practice[1,2,7,10]
  - For example, the estimated sensitivity of ICD-9 codes has been shown to vary from 27% to 50%[2]
- Hospitalization rates at year 2 were assessed following treatment at year 1 after the first NTMLD diagnosis, and compared between treatment groups. Treatment group comparisons were achieved by using a mixed-effects logistic regression to adjust for patient characteristics and health conditions measured by the Charlson Comorbidity Index during the 12 months prior to NTMLD diagnosis (baseline)

Table 1. Patient Groups According to NTMLD Treatment Regimen and Regimen Frequency

Group	Antibiotic regimen	Frequency, n	Patients, %
Group 1 (SOC)[a,b]	Azithromycin + ethambutol + rifampin	165	56
	Clarithromycin + ethambutol + rifampin	84	29
	Azithromycin + ethambutol + rifabutin	28	10
	Clarithromycin + ethambutol + rifabutin	14	5
	Azithromycin + ciprofloxacin + ethambutol + rifampin	8	3
	Azithromycin + ethambutol + moxifloxacin + rifampin	5	2
	Ciprofloxacin + clarithromycin + ethambutol + rifampin	4	1
	Azithromycin + clarithromycin + ethambutol + rifampin	3	1
	Azithromycin + ethambutol + rifabutin + rifampin	3	1
	Amikacin + azithromycin + ethambutol + rifampin	2	1
	Azithromycin + ethambutol + levofloxacin + rifampin	2	1
	Azithromycin + clarithromycin + ethambutol + rifabutin	1	0
	Azithromycin + ethambutol + levofloxacin + rifampin	1	0
	Clarithromycin + ethambutol + levofloxacin + rifampin	1	0
	Clarithromycin + ethambutol + moxifloxacin + rifabutin	1	0
	Clarithromycin + ethambutol + moxifloxacin + rifampin	1	0
	Clarithromycin + ethambutol + rifabutin + rifampin	1	0
Group 2 (Other)[a,c]	Azithromycin	141	32
	Clarithromycin	75	17
	Ethambutol	72	16
	Azithromycin + ethambutol	66	15
	Ethambutol + rifampin	43	10
	Rifampin	36	8
	Azithromycin + rifampin	34	8
	Clarithromycin + ethambutol	30	7
	Ciprofloxacin	22	5
	Clarithromycin + rifampin	18	4
	Ethambutol + rifabutin	13	3
	Rifabutin	13	3
	Azithromycin + moxifloxacin	11	2
	Moxifloxacin	11	2
	Levofloxacin	10	2
	Azithromycin + ciprofloxacin	9	2
	Azithromycin + rifabutin	8	2
	Ciprofloxacin + clarithromycin	7	2
	Clarithromycin + rifabutin	6	1
	Linezolid	6	1
	Azithromycin + ciprofloxacin + ethambutol	5	1
	Azithromycin + ethambutol + moxifloxacin	5	1
	Clarithromycin + moxifloxacin	5	1
	Amikacin + azithromycin	4	1
	Ciprofloxacin + clarithromycin + ethambutol	4	1
	Amikacin	3	1
	Azithromycin + ciprofloxacin + rifampin	3	1
	Ciprofloxacin + ethambutol	3	1
	Ethambutol + moxifloxacin	3	1
Group 3 (Untreated)	No treatment		

[a]Drug usage was evaluated during year 1.
[b]17 different drug combinations were observed across 294 patients.
[c]54 different drug combinations were observed across 447 patients; only the top 29 regimens are listed here.

Table 2. Top 3 Prescribed Immunosuppressive Therapies

Class	Drug[a]
Systemic corticosteroids	Methylprednisolone, prednisone, triamcinolone acetonide
Inhaled steroids	Budesonide/formoterol fumarate, fluticasone/salmeterol, mometasone furoate
Methotrexate	Methotrexate sodium
Miscellaneous	Azathioprine, hydroxychloroquine sulfate, leflunomide
TNF antagonists	Adalimumab, etanercept, infliximab

TNF, tumor necrosis factor.
[a]Top 3 drugs are listed within each category; other drugs included in the study are not shown.

RESULTS

- A total of 1039 patients were included in the analysis
  - 294 (28.3%) received SOC, 298 (28.7%) received Other antibiotics, and 447 (43.0%) were Untreated

Table 3. Baseline Patient Health Characteristics

	NTMLD Treatment Group		
	SOC (n=294)	Other (n=298)	Untreated (n=447)
Age, mean (SD)	65 (14.1)	64 (16.4)	71 (11.4)
Female, n (%)	196 (66.7)	306 (68.7)	321 (68.4)
Charlson Comorbidity Index, mean (SD)	1.90 (2.07)	2.09 (2.14)	2.13 (2.20)
Baseline comorbidity, n (%)			
Arrhythmia	55 (18.7)	56 (18.8)	113 (25.3)
Aspergillosis	5 (1.7)	16 (5.4)	12 (2.7)
Asthma	63 (21.4)	88 (29.5)	63 (14.1)
Atherosclerosis	16 (5.4)	20 (6.7)	35 (7.8)
Bronchiectasis	110 (37.4)	108 (36.2)	163 (36.5)
Cancer	44 (15.0)	60 (20.1)	77 (17.2)
Colitis	8 (2.7)	18 (6.0)	17 (3.8)
Congestive heart failure	28 (9.5)	32 (10.7)	56 (12.5)
COPD	147 (50.0)	159 (53.4)	213 (47.7)
Coronary artery disease	43 (14.6)	57 (19.1)	85 (19.0)
Crohn's disease	1 (0.3)	4 (1.3)	2 (0.4)
Cystic fibrosis (pulmonary)	3 (1.0)	15 (5.0)	3 (0.7)
Dementia	2 (0.7)	0 (0.0)	6 (1.3)
Depression	33 (11.2)	34 (11.4)	31 (6.9)
Diabetes	50 (17.0)	43 (14.4)	58 (13.0)
GERD	72 (24.5)	77 (25.8)	91 (20.4)
Heart valve disorder	43 (14.6)	45 (15.1)	67 (15.0)
HIV	5 (1.7)	10 (3.4)	5 (1.1)
Hyperlipidemia	120 (40.8)	137 (46.0)	221 (49.4)
Hypertension	130 (44.2)	130 (43.6)	227 (50.8)
Idiopathic pulmonary fibrosis	4 (1.4)	4 (1.3)	7 (1.6)
Immune deficiency	22 (7.5)	27 (9.1)	21 (4.7)
Lung cancer	12 (4.1)	21 (7.1)	23 (5.2)
Lupus	1 (0.3)	1 (0.3)	4 (0.9)
Mental disorder	53 (18.0)	52 (17.4)	64 (14.3)
Metastatic carcinoma	7 (2.4)	2 (0.7)	14 (3.1)
Moderate or severe liver disease	1 (0.3)	2 (0.7)	4 (0.9)
Multiple sclerosis	2 (0.7)	0 (0.0)	0 (0.0)
Myocardial infarction	12 (4.1)	10 (3.4)	22 (4.9)
Obesity	13 (4.4)	15 (5.0)	7 (1.6)
Organ transplant	3 (1.0)	6 (2.0)	5 (1.1)
Pectum excavatum	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	148 (50.3)	128 (43.0)	156 (34.9)
Psoriasis	3 (1.0)	9 (3.0)	6 (1.3)
Pulmonary arterial hypertension	18 (6.1)	11 (3.7)	31 (6.9)
Rheumatoid disease	11 (3.7)	18 (6.0)	32 (7.2)
Sjögren's syndrome	3 (1.0)	1 (0.3)	2 (0.4)
Tobacco use	65 (22.1)	65 (21.8)	73 (16.3)
Tuberculosis	26 (8.8)	28 (9.4)	27 (6.0)
Immunosuppressant drug use, n (%)	187 (63.6)	184 (61.7)	175 (39.1)
Infecting *Mycobacterium*, n (%) *M abscessus*[a]	0 (0.0)	12 (4.0)	3 (0.7)

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus.
[a]*M abscessus* was defined according to the following treatment drugs: imipenem, meropenem, tigecycline, and cefoxitin. The search for therapies to define *M abscessus* was conducted for both baseline and year 1 to account for the possibility of treatment being claimed before NTMLD diagnosis is recorded.

Baseline Demographic Characteristics and Health Conditions

- Demographic characteristics were comparable across all treatment groups (**Table 3**)
  - Patients who received no treatment for NTMLD were older than those who received treatment (mean age of 71 years compared with 65 years and 64 years in SOC and Other groups, respectively)
  - Women comprised the majority of patients across all treatment groups
- At baseline, there was no difference in Charlson Comorbidity Index score between treatment groups
  - However, comorbidity distribution differed prominently in asthma (SOC 21.4%, Other 29.5%, and Untreated 14.1%), arrhythmia (SOC 18.7%, Other 18.8%, and Untreated 25.3%), cystic fibrosis (SOC 1.0%, Other 5.0%, and Untreated 0.7%), immune deficiency (SOC 7.5%, Other 9.1%, and Untreated 4.7%), pneumonia (SOC 50.3%, Other 43.0%, and Untreated 34.9%), and tuberculosis (SOC 8.8%, Other 9.4%, and Untreated 6.0%), and in immunosuppressant use (SOC 63.6%, Other 61.7%, and Untreated 39.1%)
- Use of concomitant immunosuppressive and/or biologic agents was similar across all treatment groups, with the exception of a lower proportion of untreated patients using systemic or inhaled corticosteroids (**Table 4**)

Table 4. Baseline Immunosuppressant Use

	NTMLD Treatment Group		
Immunosuppressant drug use, n (%)	SOC (n=294)	Other (n=298)	Untreated (n=447)
Corticosteroids			
Inhaled	114 (38.8)	111 (37.2)	97 (21.7)
Intra-articular	0 (0.0)	0 (0.0)	0 (0.0)
Systemic	146 (49.7)	157 (52.7)	133 (29.8)
JAK inhibitor	0 (0.0)	0 (0.0)	0 (0.0)
Methotrexate	5 (1.7)	5 (1.7)	10 (2.2)
Miscellaneous immunosuppressants	15 (5.1)	19 (6.4)	18 (4.0)
TNF antagonist	5 (1.7)	5 (1.7)	3 (0.7)

JAK, Janus kinase.

Observed Hospitalization Rates at Baseline, Year 1, and Year 2 by Treatment Group

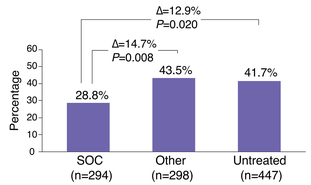
- The proportion of patients who were hospitalized at baseline was 33.0% in the SOC group, 31.5% in the Other group, and 28.2% in the Untreated group
- The proportion of patients who were hospitalized at year 1 was 34.7% in the SOC group, 41.9% in the Other group, and 30.9% in the Untreated group
- The proportion of patients who were hospitalized at year 2 was 18.7% in the SOC group, 26.2% in the Other group, and 23.7% in the Untreated group
- While hospitalization rate was higher in the SOC group at baseline before NTMLD diagnosis, we observed a lower rate of hospitalization in the SOC group compared to the Other or Untreated group at year 2 following year 1 treatment

Note: Treatment was classified at year 1 and hospitalization rate was observed at year 2 as an outcome measure of year 1 treatment. Adjusted hospitalization rates between treatment groups were derived by modeling hospitalization event at year 2 accounting for baseline patient characteristics listed in Table 3.

Adjusted Hospitalization Rates at Year 2 by Treatment Group (Figure 1)

- Adjusted hospitalization rates, which represent the probability of being hospitalized, were 28.8% (95% CI: 13.7%-50.8%) for the SOC group, 43.5% (24.3%-64.9%) for the Other group, and 41.7% (21.8%-64.6%) for the Untreated group in year 2
- Comparison of SOC vs other antibiotic therapies revealed a significantly lower risk of all-cause hospitalization after adjustment (odds ratio [OR]=0.53; 95% CI, 0.33-0.85, *P*=0.008)
- Comparison of SOC vs Untreated patients also revealed a significantly lower risk of all-cause hospitalization after adjustment (OR=0.57; 95% CI, 0.35-0.91, *P*=0.020)
- In addition, a sensitivity analysis that excluded patients with CF revealed a significantly lower risk of all-cause hospitalization in the SOC group compared with the Other and Untreated groups
  - SOC group vs Other group: OR=0.49 (95% CI, 0.30-0.81, *P*=0.005)
  - SOC group vs Untreated group: OR=0.57 (95% CI, 0.35-0.93, *P*=0.024)

Figure 1. Adjusted All–Cause Hospitalization Rate at Year 2 After NTMLD Diagnosis by Treatment Group



CONCLUSIONS

- Fewer than one-third of patients in our sample received an antibiotic regimen consistent with current ATS/IDSA guidelines, while use of alternate regimens was common among treated patients and a considerable proportion of patients were untreated
  - This finding is consistent with previous findings of poor adherence to treatment guidelines for NTMLD among US physicians[11]
- We observed a significantly lower hospitalization rate at year 2 in NTMLD patients receiving antibiotics at year 1 that were concordant with first-line ATS/IDSA guideline recommendations compared with those who used other antibiotic regimens
- Despite a lower pulmonary disease burden at baseline, the Untreated group also showed a higher rate of hospitalization than the SOC group at year 2
- Given the increasing hospitalization rates and costs associated with NTMLD in the United States,[9] these results reinforce the importance of using guideline-recommended antibiotic regimens for managing this potentially debilitating disease

REFERENCES

1. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in US Medicare beneficiaries. *Am J Respir Crit Care Med*. 2012;185(8):881-886. **2.** Prevots DR, Marras TK. Epidemiology of human pulmonary infection with non-tuberculous mycobacteria: a review. *Clin Chest Med*. 2015;36(1):13-34. **3.** Park HY, Jeong BH, Chon HR, Jeon K, Daley CL, Koh WJ. Lung function decline according to clinical course in nontuberculous mycobacterial disease. *Chest*. 2016;150(6):1222-1232. **4.** Mehta M, Marras TK. Impaired health-related quality of life in pulmonary nontuberculous mycobacterial disease. *Respir Med*. 2011;105(11):1718-1725. **5.** Novosad SA, Henkle E, Schafer S, et al. Mortality after respiratory isolation of nontuberculous mycobacteria: a comparison of patients who did and did not meet disease criteria. *Ann Am Thorac Soc*. 2017;14(7):1112-1119. **6.** Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175(4):367-416. **7.** Strollo SE, Adjemian J, Adjemian MK, Prevots DR. The burden of pulmonary nontuberculous mycobacterial disease in the United States. *Ann Am Thorac Soc*. 2015;12(10):1458-1464. **8.** Aksamit TR, O'Donnell AE, Barker A, et al. Adult patients with bronchiectasis: a first look at the US Bronchiectasis Research Registry. *Chest*. 2017;151(5):982-992. **9.** Mirsaeidi M, Allen MB, Ebrahimi G, Schraufnagel D. Hospital costs in the US for pulmonary mycobacterial disease. *Int J Mycobacteriol*. 2015;4(3):217-221. **10.** Prevots DR, Shaw PA, Strickland D, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. *Am J Respir Crit Care Med*. 2010;182(7):970-976. **11.** Adjemian J, Prevots DR, Gallagher J, Heap K, Gupta R, Griffith D. Lack of adherence to evidence-based treatment guidelines for nontuberculous mycobacterial lung disease. *Ann Am Thorac Soc*. 2014;11(1):9-16.

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