Poster Number 2272

Healthcare Resource Utilization and Costs Following Diagnosis of Nontuberculous Mycobacterial Lung Disease in the US

Theodore K. Marras, MD[1]; Mehdi Mirsaeidi, MD, MPH[2]; Engels Chou, MS[3]; Gina Eagle, MD[3]; Raymond Zhang, MS[4]; Ping Wang, PhD[3]; and Quanwu Zhang, PhD[3]

[1]Toronto Western Hospital, Toronto, ON, Canada; [2]University of Miami, Coral Gables, FL; [3]Insmed Incorporated, Bridgewater, NJ; [4]Orbis Data Solutions, Woburn, MA

BACKGROUND

- Nontuberculous mycobacterial lung disease (NTMLD) is gaining recognition as an important public health concern due to its increasing prevalence in recent decades[1-3]
- The high morbidity and mortality rates of NTMLD create a substantial burden on patients, the healthcare system, and financial resources[4-9]
- The slow progression and chronic and recurring nature of NTMLD, combined with the lengthy treatment required, results in significant healthcare costs due to antibiotics and hospitalizations[10,11]
- Despite increasing awareness of NTMLD, reports on the economic impact of healthcare resource utilization (HCRU) and costs are limited

OBJECTIVE

- To estimate HCRU and payer costs associated with NTMLD in the United States from a 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
  - A control group was randomly selected from the plan members without NTMLD and matched 2:1 to the NTMLD sample by age, sex, and insurance coverage period
- NTMLD diagnosis dates were assigned to matched controls as the index date for the assessment of HCRU and its associated costs at year 1 and year 2 after the index date
  - Note that the majority of NTMLD cases in the United States (64%-85%) are known to be caused by *Mycobacterium avium* complex (MAC) infection[3]
  - NTMLD caused by *Mycobacterium abscessus* infection is more difficult to treat due to antibiotic resistance,[12] and has been reported to have a higher projected treatment cost compared with other strains of NTM[11]
- HCRU and standardized costs were summarized over 12 months (baseline) before NTMLD diagnosis and for 2 subsequent years
  - Values were standardized using the resource-based relative value scale (RBRVS), which is broadly used by managed care and Medicare organizations to make reimbursement decisions for physician claims
- Utilization data and direct costs paid by payers were abstracted from database claims
  - Utilization data included number of hospitalizations, length of hospital stay, emergency room (ER) visits, outpatient visits, and the number of ancillary care claims
  - Ancillary care was defined as any use of medical equipment, home health or hospice visits, services and supplies, and transportation services
  - To benchmark the cost burden of NTMLD, we also extracted the costs of several other pulmonary diseases (chronic obstructive pulmonary disease [COPD], idiopathic pulmonary fibrosis [IPF], pulmonary arterial hypertension [PAH], and lung cancer) from claims of patients with 24 months of continuous enrollment (n=2005)
- Patient comorbidities were identified using ICD-9 or ICD-10 codes, and use of select immunosuppressive therapies were identified through pharmacy dispensing claims (**Table 1**)

Table 1. 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 immunosuppressants	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.

- Resource use and costs are likely to be underestimated due to an overall tendency of undertesting and undercoding for NTMLD in clinical practice[1,3,10,13]
  - For example, the estimated sensitivity of ICD-9 codes has been shown to vary from 27% to 50%[3]
- HCRU over year 1 and year 2 following the diagnosis of NTMLD was estimated between the NTMLD and matched control cohorts, with adjustments for age, sex, Charlson Comorbidity Index, *M abscessus* infection, geographic location (ie, state), and baseline healthcare conditions as covariates
  - A mixed-effects regression model was used to account for the extraneous influence of health factors on the cost comparisons that were not attributable to NTMLD (eg, preexisting baseline conditions) and to calculate adjusted HCRU and cost values
- In addition, the first-year total healthcare costs of patients after the diagnosis of NTMLD was summarized vis-a-vis patient cohorts of COPD, IPF, PAH, and lung cancer to estimate economic burden of the diseases. These patient cohorts were required to have at least 12 months of health insurance coverage before and after the first disease diagnosis

Table 2. Demographics and Baseline Patient Health Characteristics

	Patients with NTMLD (n=1039)	Controls (n=2078)
Age, mean (SD)	68 (14.1)	68 (14.1)
Female, n (%)	699 (67.0)	1392 (67.0)
Charlson Comorbidity Index, mean (SD)	2.0 (2.16)	0.5 (1.25)
Baseline patient health conditions, n (%)		
Arrhythmia	224 (21.6)	130 (6.3)
Aspergillosis	33 (3.2)	0 (0.0)
Asthma	214 (20.6)	73 (3.5)
Atherosclerosis	71 (6.8)	41 (2.0)
Bronchiectasis	381 (36.7)	7 (0.3)
Cancer	181 (17.4)	110 (5.3)
Colitis	43 (4.1)	16 (0.8)
Congestive heart failure	116 (11.2)	85 (4.1)
COPD	519 (50.0)	124 (6.0)
Coronary artery disease	185 (17.8)	146 (7.0)
Crohn's disease	7 (0.7)	2 (0.1)
Cystic fibrosis (pulmonary)	21 (2.0)	0 (0.0)
Dementia	8 (0.8)	19 (0.9)
Depression	98 (9.4)	72 (3.5)
Diabetes	151 (14.5)	224 (10.8)
GERD	240 (23.1)	154 (7.4)
Heart valve disorder	155 (14.9)	82 (4.0)
HIV	20 (1.9)	0 (0.0)
Hyperlipidemia	478 (46.0)	579 (27.9)
Hypertension	487 (46.9)	611 (29.4)
Idiopathic pulmonary fibrosis	15 (1.4)	1 (0.0)
Immune deficiency	70 (6.7)	10 (0.5)
Lung cancer	56 (5.4)	5 (0.2)
Lupus	6 (0.6)	3 (0.1)
Mental disorder	169 (16.3)	154 (7.4)
Metastatic carcinoma	23 (2.2)	13 (0.6)
Moderate or severe liver disease	7 (0.7)	5 (0.2)
Multiple sclerosis	2 (0.2)	8 (0.4)
Myocardial infarction	44 (4.2)	29 (1.4)
Obesity	35 (3.4)	70 (3.4)
Organ transplant	14 (1.3)	2 (0.1)
Pectum excavatum	0 (0.0)	0 (0.0)
Pneumonia	432 (41.6)	29 (1.4)
Psoriasis	18 (1.7)	13 (0.6)
Pulmonary arterial hypertension	60 (5.8)	22 (1.1)
Rheumatoid disease	61 (5.9)	21 (1.0)
Sjögren's syndrome	6 (0.6)	2 (0.1)
Tobacco use	203 (19.5)	75 (27.0)
Tuberculosis	81 (7.8)	0 (0.0)
Immunosuppressant drug use, n (%)	546 (52.6)	271 (13.0)
Infecting *Mycobacterium*, n (%) *M abscessus*[a]	15 (1.4)	0 (0.0)

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.

RESULTS

- A total of 1039 patients were included in the NTMLD cohort and 2078 in the control cohort

Demographics and Baseline Disease Characteristics

- Demographic characteristics were comparable across cohorts, with an average age of 68 years and the majority of subjects female (**Table 2**)
- Use of immunosuppressive therapies was nearly 4 times greater among patients with NTMLD compared with controls (**Table 3**)
- Patients with NTMLD had a higher Charlson Comorbidity Index score and more health disorders (2.0 [±2.2]) than controls (0.5 [±1.3]) at baseline (**Table 2**)
  - Compared with controls, the NTMLD population had a higher prevalence of respiratory disorders (20.6% vs 3.5% for asthma, 36.7% vs 0.3% for bronchiectasis, 50.0% vs 6.0% for COPD, 2.0% vs 0.0% for cystic fibrosis, 41.6% vs 1.4% for pneumonia, 7.8% vs 0.0% for tuberculosis) and greater immunosuppressant drug use (52.6% vs 13.0%). About 80% of the NTMLD cohort had at least one medical claim for a pulmonary disorder.

Table 3. Baseline Immunosuppressant Use

Immunosuppressant drug use, n (%)	Patients with NTMLD (n=1039)	Controls (n=2078)
Corticosteroids		
Inhaled	322 (31.0)	82 (3.9)
Intra-articular	0 (0.0)	0 (0.0)
Systemic	436 (42.0)	222 (10.7)
JAK inhibitor	0 (0.0)	0 (0.0)
Methotrexate	20 (1.9)	7 (0.3)
Miscellaneous immunosuppressants	52 (5.0)	7 (0.3)
TNF antagonist	13 (1.3)	4 (0.2)

JAK, janus kinase.

Adjusted Hospitalization Rates (Table 4)

- NTMLD patients had a 55.0% risk of hospitalization in year 1 (95% CI, 45.4-64.3) and a 38.8% risk in year 2 (95% CI, 30.0-48.4)
- The matched control patients had a 20.9% risk of hospitalization in year 1 (95% CI, 14.9-28.4) and a 21.9% risk in year 2 (95% CI, 15.7-29.6)
- The NTMLD group had a 464% risk of hospitalization in year 1 compared with the matched control group (odds ratio [OR]=4.64; 95% CI, 3.74-5.76; *P*<0.001), and a 226% risk in year 2 (OR=2.26; 95% CI, 1.78-2.87; *P*<0.001)

Table 4. Adjusted Mean Hospitalization Rates for Follow–up Years 1 and 2

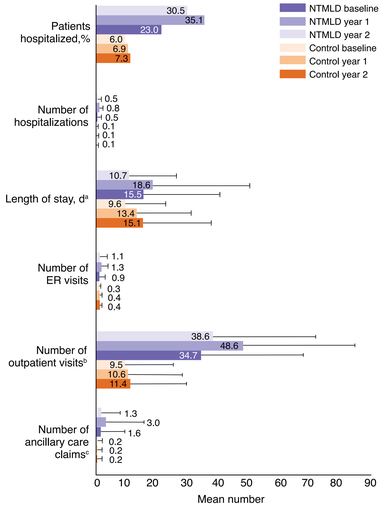
	Year 1		Year 2	
	Patients with NTMLD (n=1039)	Controls (n=2078)	Patients with NTMLD (n=1039)	Controls (n=2078)
Adjusted mean hospitalization rate, %				
LSM (SE)	55.0 (4.9)	20.9 (3.4)	38.8 (4.7)	21.9 (3.6)
95% CI	45.4-64.3	14.9-28.4	30.0-48.4	15.7-29.6

LSM, least squares mean.

Observed HCRU (Figure 1)

- Patients with NTMLD had higher hospitalization rates, higher average number of hospitalizations, and longer hospital stays compared with controls at baseline and at each follow-up year
- The mean number of ER visits in the NTMLD cohort increased by 18% from baseline to year 1, but decreased below the baseline level in year 2
- Similarly, the number of outpatient visits among NTMLD patients increased by 26% in the first year but decreased below baseline in year 2
- The average number of claims for ancillary care by patients with NTMLD more than doubled from baseline to year 1 and returned near the baseline level in year 2

Figure 1. Observed Overall HCRU by Group at Baseline and During Follow–Up



Values presented are per patient unless otherwise specified.
[a]Mean length of stay based on patients who were hospitalized.
[b]Outpatient visits included facilities (eg, laboratory, radiology) and professional services (eg, pathology, immunizations and injections, rehabilitation).
[c]Ancillary care included services for medical equipment, home health/hospice visits, services and supplies, and transportation services.

Appendix Table. Observed Median (Q1, Q3) Direct Healthcare Costs ($) of NTMLD and Control Cohorts at Baseline and Follow–up

	Baseline		Year 1		Year 2	
	Patients with NTMLD (n=1039)	Controls (n=2078)	Patients with NTMLD (n=1039)	Controls (n=2078)	Patients with NTMLD (n=1039)	Controls (n=2078)
Total costs[a]	15,493 (6349, 37,015)	587 (0, 3983)	18,626 (8012, 52,891)	745 (0, 5092)	11,385 (3128, 31,172)	819 (0, 5126)
Pharmacy costs	2209 (556, 6185)	21 (0, 1080)	3957 (1491, 10,003)	45 (0, 1145)	2418 (171, 7390)	55 (0, 1309)
Drug administration costs	9 (0, 389)	0 (0, 0)	16 (0, 593)	0 (0, 0)	0 (0, 192)	0 (0, 0)
Medical costs[a]	11,701 (3821, 27,843)	209 (0, 2258)	12,416 (4704, 37,141)	288 (0, 3029)	6715 (1770, 20,558)	400 (0, 2972)
Hospitalization costs	0 (0, 8056)	0 (0, 0)	0 (0, 13,494)	0 (0, 0)	0 (0, 0)	0 (0, 0)
ER costs	0 (0, 1063)	0 (0, 0)	0 (0, 1287)	0 (0, 0)	0 (0, 498)	0 (0, 0)
Outpatient costs[b]	7199 (2800, 14,864)	194 (0, 1929)	7701 (3699, 15,709)	255 (0, 2352)	4878 (1402, 11,433)	372 (0, 2466)
Ancillary costs[c]	0 (0, 0)	0 (0, 0)	0 (0, 68)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Q1, first quartile; Q3, third quartile.
[a]Total insurance costs = pharmacy costs + medical costs; medical costs = inpatient hospitalization costs + ER costs + outpatient/office visit costs + ancillary care costs.
[b]Outpatient included facilities (eg, laboratory, radiology) and professional services (eg, pathology, immunizations and injections, rehabilitation).
[c]Ancillary care included services for medical equipment, home health/hospice visits, services and supplies, and transportation services.

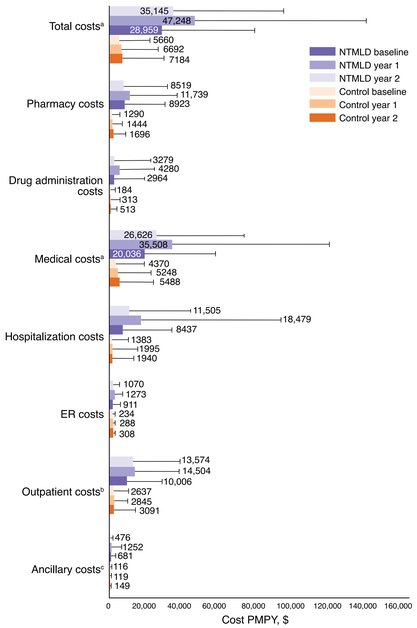
Costs

- Total annual healthcare insurance spending, including medical and pharmacy insurance costs, was substantially higher in patients with NTMLD than in controls at each yearly timepoint (**Figure 2** and **Appendix Table**)
- Total direct healthcare costs in the NTMLD cohort remained significantly higher than the control cohort after adjustment (**Table 5**)
  - In year 1, costs for the NTMLD patient population that included and adjusted for patients with cystic fibrosis (CF) were $74,255 (95% CI, $67,239-$81,271) and $30,075 (95% CI, $21,360-$38,791) for the matched control with a cost difference of $44,180 (95% CI, $37,663-$50,697)
    - Removing CF patients, the cost difference was $49,611 (95% CI, $42,002-$57,221) between NTMLD and match control group
  - In year 2, costs for the NTMLD patient population that included and adjusted for patients with CF were $50,263 (95% CI, $43,686-$56,840) and $30,677 (95% CI, $22,134-$39,220) for matched control group with a cost difference of $19,586 (95% CI, $13,796-$25,375)
    - Removing CF patients, the cost difference was $15,126 (95% CI, $8,727-$21,524)
  - From year 1 to year 2, total adjusted costs for NTMLD patients decreased by $23,992 (32.3%) when adjusted for CF and $33,884 (55.1%) when CF patients were removed
  - First-year insurance/payer spending per patient with NTMLD ($48,169) was comparable to the spending on patients with other severe respiratory diseases who were randomly sampled from the general population of the managed care insurance plan, including COPD ($22,901), idiopathic pulmonary fibrosis ($44,313), pulmonary arterial hypertension ($51,753), and lung cancer ($69,005)

Table 5. Adjusted Total Direct Healthcare Costs of NTMLD and Control Cohorts Across Years 1 and 2

	Year 1		Year 2	
Total adjusted healthcare costs, $	Patients with NTMLD (n=1039)	Controls (n=2078)	Patients with NTMLD (n=1039)	Controls (n=2078)
With CF				
LSM (SE)	74,255 (3578)	30,075 (4445)	50,263 (3354)	30,677 (4357)
95% CI	67,239-81,271	21,360-38,791	43,686-56,840	22,134-39,220
Without CF				
LSM (SE)	61,540 (3541)	11,929 (1910)	27,656 (2992)	12,531 (1680)
95% CI	54,598-68,483	8185-15,673	21,790-33,523	9237-15,825

Figure 2. Observed Mean Direct Healthcare Costs



PMPY, per member per year.
[a]Total insurance costs = pharmacy costs + medical costs; medical costs = inpatient hospitalization costs + ER costs + outpatient/office visit costs + ancillary care costs.
[b]Outpatient included facilities (eg, laboratory, radiology) and professional services (eg, pathology, immunizations and injections, rehabilitation).
[c]Ancillary care included services for medical equipment, home health/hospice visits, services and supplies, and transportation services.

CONCLUSIONS

- Observed HCRU and payer costs were higher in patients with NTMLD compared with controls across the 36-month observation period in our sample of commercially insured and Medicare Advantage plan patients
  - Patients with NTMLD cost approximately 5 times more than controls at baseline and year 1
- We observed an increase in HCRU and costs from baseline to year 1 followed by a decrease from year 1 to year 2 in the NTMLD cohort but not in the control cohort
  - The reversed U-shape of total costs in patients with NTMLD may reflect joint economic outcomes of disease, comorbidity, and management
- Our findings highlight the costly burden of patients with NTMLD in the United States, both in resource utilization by patients and relative costs to payers
- Overall, HCRU and insurance spending associated with NTMLD represent a substantial economic burden to the patient and payer
- The study also showed a cost reduction in the NTMLD patient population from year 1 to year 2, suggesting a potential economic benefit of patient treatment, which is further investigated in a separate study

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.** Marras TK, Mendelson D, Marchand-Austin A, May K, Jamieson FB. Pulmonary nontuberculous mycobacterial disease, Ontario, Canada, 1998-2010. *Emerg Infect Dis*. 2013;19(11):1889-1891. **3.** Prevots DR, Marras TK. Epidemiology of human pulmonary infection with non-tuberculous mycobacteria: a review. *Clin Chest Med*. 2015;36(1):13-34. **4.** Park HY, Jeong BH, Chon HR, Jeon K, Daley CL, Koh WJ. Lung function decline according to clinical course in nontuberculous mycobacterial lung disease. *Chest*. 2016;150(6):1222-1232. **5.** O'Connell ML, Birkenkamp KE, Kleiner DE, Folio LR, Holland SM, Olivier KN. Lung manifestations in an autopsy-based series of pulmonary or disseminated nontuberculous mycobacterial disease. *Chest*. 2012;141(5):1203-1209. **6.** 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. **7.** Yeh JJ, Wang YC, Lin CL, et al. Nontuberculous mycobacterial infection is associated with increased respiratory failure: a nationwide cohort study. *PLoS One*. 2014;9(6):e99260. doi:10.1371/journal.pone.0099260. **8.** van der Laan R, Obradovic M. Mortality in patients with *Mycobacterium avium* complex lung disease–a review of published literature. Poster presented at: 58th Congress of the Germany Society of Pulmonology and Respiratory Medicine; March 22-25, 2017; Stuttgart, Germany. **9.** 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. **10.** 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. **11.** Ballarino GJ, Olivier KN, Claypool RJ, Holland SM, Prevots DR. Pulmonary nontuberculous mycobacterial infections: antibiotic treatment and associated costs. *Respir Med*. 2009;103(10):1448-1455. **12.** 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. **13.** 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.

Poster presented at IDWeek™ 2017 • October 2–8, 2017 • San Diego, CA