Nontuberculous mycobacterial pulmonary disease incidence among elderly patients with bronchiectasis

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To the Editor:

Nontuberculous mycobacteria (NTM) are environmental pathogens causing disease in humans; however, not everyone exposed develops disease [1]. Those with underlying pulmonary diseases, persons over 60 years old and women have an increased risk for nontuberculous mycobacterial pulmonary disease (NTM-PD) [1, 2]. Bronchiectasis is a lung condition characterised by chronic airway dilation and inflammation, resulting in impaired mucus clearance, and is associated with NTM-PD [1–3]. Both NTM-PD and bronchiectasis are increasing in incidence in the USA [2, 3]. Although patients with bronchiectasis are at increased risk of acquiring NTM-PD [1, 2], the incidence of NTM-PD in these patients is not well described. Previous US Medicare data estimated those with bronchiectasis were 50- to 75-fold more likely to have a diagnosis of NTM-PD than those without bronchiectasis [4]. The objective of this analysis was to estimate the incidence of NTM-PD among US Medicare enrolees newly diagnosed with bronchiectasis over the age of 65 years.

We identified a cohort of newly diagnosed ("incident") bronchiectasis patients in a dataset used for prior analysis [5]. Briefly, we obtained a cohort of US Medicare enrolees with an International Classification of Disease, Ninth Revision Clinical Modification (ICD-9-CM) diagnosis of bronchiectasis (494.0 or 494.1) given by a pulmonologist between 2006 and 2014 [6]. We included enrolees covered by Parts A (hospital insurance), B (medical insurance) and D (prescription drug plans), excluding C (Medicare advantage plans) [7]. We excluded patients aged <65 years and those with cystic fibrosis, HIV infection and organ transplantation. The incident bronchiectasis diagnosis index date was the date of first diagnosis after 12 months of observation and no prior bronchiectasis diagnosis. Last, we excluded those with NTM-PD history <12 months prior to bronchiectasis diagnosis date.

We defined our outcome of incident NTM-PD by 1) diagnostic claim alone, ICD-9-CM 031.0 given by a provider (n=8489), or 2) diagnostic claim with or without evidence of NTM-PD treatment with a macrolide-based multi-drug regimen (defined as azithromycin or clarithromycin use with either ethambutol, a rifamycin or a fluoroquinolone for ≥28 days concomitantly) within the prior 12 months (n=10 289). We defined COPD/emphysema as two ambulatory visits or one in-patient admission with ICD-9-CM diagnostic claims of 491.xx, 492.xx, 493.2 or 496.xx [6].

We first described patient demographics, clinical characteristics and healthcare utilisation during the baseline 12 months prior to their bronchiectasis index date. We compared those with and without incident NTM-PD using t-tests for continuous data and chi-square tests for categorical data. We calculated the incidence rates of NTM-PD per 100 000 person-years occurring after the bronchiectasis index date and stratified by patient characteristics of interest. The numerator comprised newly diagnosed NTM-PD ("incident") cases and the denominator comprised total person-years after the index date and censored at time of NTM-PD diagnosis, death or end of observation. We calculated incidence rate ratios (IRRs) and 95% confidence intervals of both NTM-PD definitions by sex, age group, COPD diagnosis yes *versus* no, and race/ethnicity. In a sensitivity analysis to account for the possibility of "concurrent" NTM-PD and bronchiectasis diagnosis in some patients, we excluded those with NTM-PD diagnosis within 6 months of their bronchiectasis index date. Statistical analysis was completed using STATA software (College Station, TX, USA).

Shareable abstract (@ERSpublications)
Incidence of NTM-PD was estimated among US Medicare beneficiaries newly diagnosed with bronchiectasis between 2006 and 2014. Overall incidence of NTM-PD was found to be as high as 1950 per 100 000 person-years. https://bit.ly/3iAr4o5

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TABLE 1 Cohort demographics, incidence of nontuberculous mycobacterial pulmonary disease (NTM-PD) by two case definitions of NTM-PD, and NTM-PD incidence rate ratios by patient characteristics

Variables	Incident NTM-PD cohort	Bronchiectasis and no NTM-PD cohort	NTM-PD case definition 1[#]	IRR[¶]	95% CI	NTM-PD case definition 2[+]	IRR	95% CI
Overall	10 289	161 874	1600			1950		
NTM-PD diagnosis at 6-months or later	5198	161 874				978		
Sex								
Females	7972 (77.5)	102 946 (63.6)	1880	1.81	1.72–1.91	2260	1.73	1.65–1.81
Males	2317 (22.5)	58 928 (36.4)	1040			1310		
Age category								
65–69 years	2275 (22.1)	32 696 (20.2)	1540			1910		
70–74 years	2407 (23.4)	38 010 (23.5)	1520	0.99	0.92–1.05	1850	0.97	0.91–1.02
75–79 years	2447 (23.8)	36 515 (22.5)	1620	1.05	0.98–1.12	1970	1.03	0.98–1.10
⩾80 years	3160 (30.7)	54 653 (33.8)	1690	1.09	1.03–1.16	2000	1.05	0.99–1.11
COPD diagnosis								
COPD	3935 (38.2)	84 072 (51.9)	1250	0.58	0.56–0.61	1570	0.62	0.60–0.64
No COPD	6354 (61.8)	77 802 (48.1)	2150			2540		
Race and ethnicity								
American Indian or Alaska native	15 (0.1)	611 (0.4)	767	0.46	0.25–0.77	822	0.41	0.23–0.67
Asian/Pacific Islander	544 (5.3)	6296 (3.9)	2037	1.22	1.10–1.34	2507	1.24	1.14–1.35
Black	211 (2.1)	8046 (4.9)	705	0.42	0.36–0.49	846	0.42	0.36–0.48
Hispanic	408 (4.0)	9607 (5.9)	985	0.59	0.52–0.66	1284	0.64	0.57–0.70
Other	84 (0.8)	1231 (0.8)	1731	1.04	0.81–1.32	2048	1.01	0.81–1.26
Unknown	15 (0.1)	327 (0.2)	1551	0.93	0.46–1.66	2115	1.05	0.59–1.73
White (non-Hispanic)	9012 (87.6)	135,757 (83.9)	1671			2018		
Baseline patient characteristics								
Comorbidities[§,f]								
Allergic bronchopulmonary aspergillosis	56 (0.5)	726 (0.5)						
Alpha-1 antitrypsin deficiency	18 (0.2)	335 (0.2)						
Asthma	**2189 (21.3)**	**46 581 (28.8)**						
Interstitial lung disease	**234 (2.3)**	**7765 (4.8)**						
Lung cancer	**286 (2.8)**	**5990 (3.7)**						
Primary ciliary dyskinesia	9 (0.1)	113 (0.1)						
Primary immune deficiency	324 (3.1)	4537 (2.8)						
Pseudomonas infection	336 (3.3)	5601 (3.5)						
Rheumatoid arthritis	**365 (3.5)**	**7301 (4.5)**						
Silicosis	8 (0.1)	194 (0.1)						
Baseline[§,f] medication use								
Home oxygen therapy prescription	**1168 (11.4)**	**39 429 (24.4)**						
Inhaled antibiotic prescription	76 (0.7)	1350 (0.8)						
ICS	**582 (5.6)**	**11 158 (6.9)**						
Corticosteroids	**2251 (21.9)**	**50 248 (31.0)**						
Nebuliser use	**1571 (15.3)**	**40 967 (25.3)**						

Incidences are reported per 100 000 person-years. Descriptive characteristics are reported as total number and proportion. IRR: incidence rate ratio; ICS: inhaled corticosteroids. [#]: incidence rate of NTM-PD diagnostic claim. [¶]: IRRs comparing within group (*e.g.* female *versus* male); referent groups noted in italics. [+]: incidence rate of NTM-PD diagnostic claim with or without treatment. [§]: baseline 12 months prior to bronchiectasis index date. [f]: significant comorbidities and medications in bold.

The incident bronchiectasis cohort comprised 172 163 patients at risk for NTM-PD. Of those, 10 289 (6%) had an NTM-PD diagnostic claim with or without treatment over the 8-year observation period. Those with incident NTM-PD were more frequently female (77.5% *versus* 63.6%; p<0.001) and white (non-Hispanic) (87.6% *versus* 83.9%; p<0.001). Those with incident NTM-PD were less likely to have a baseline COPD diagnosis (38.2% *versus* 51.9% without NTM-PD; p<0.001). Those with incident NTM-PD had fewer baseline inpatient admissions (defined as two or greater) compared to those without NTM-PD (9.9% *versus* 18.7%, p<0.001).

The overall incidence of NTM-PD diagnostic claim alone was 1600 per 100 000 person-years and 1950 per 100 000 person-years for the diagnostic claim with or without treatment definition (table 1). Results for the latter definition are further described herein. NTM-PD incidence decreased to 978 per 100 000 person-years after excluding those who were diagnosed with NTM-PD within 6 months after their bronchiectasis index date. Incidence for women was 2260 per 100 000 *versus* 1310 per 100 000 person-years for men (IRR 1.73, 95% CI 1.65–1.81). Incidence increased with age, reaching 2000 per 100 000 in those >80 years *versus* 1910 per 100 000 person-years in those 65–69 years (IRR 1.05, 95% CI 0.99–1.11). Incidence was lower for those without baseline COPD: 2540 per 100 000 *versus* 1570 per 100 000 person-years in those with COPD (IRR 0.62, 95% CI 0.60–0.64). Asian/Pacific Islanders had the highest incidence: 2507 per 100 000 *versus* 2018 per 100 000 person-years in white enrolees (IRR 1.24, 95% CI 1.14–1.35).

Our analysis of Medicare data suggests that up to 6% of bronchiectasis patients >65 years of age will be diagnosed with NTM-PD in the 8 years after their bronchiectasis diagnosis. We calculated a high incidence of NTM-PD diagnosis after bronchiectasis diagnosis in older adults with bronchiectasis: 1600 to 1950 per 100 000 person-years, depending on the case definition. After excluding possibly concurrent NTM-PD and bronchiectasis diagnoses, incidence remained high at 978 per 100 000 person-years. In a US study that included all adults in a managed care plan, NTM-PD incidence was much lower, increasing to 18.37 per 100 000 person-years among adults 65 years and older in 2015 [2]. Similar to prior studies, the incidence of NTM-PD in our study was higher among women and Asian/Pacific Islanders, and increased with age [2, 8].

NTM-PD can cause bronchiectasis and bronchiectasis increases the risk of NTM-PD [2, 3]. Bronchiectasis may develop after continued infection and inflammation [3]. Given that NTM-PD is a slowly developing infection, it can be difficult in some cases to ascertain whether it followed or alternatively preceded the development of bronchiectasis. Accordingly, we tried to overcome this limitation somewhat with our sensitivity analysis that evaluated only those who developed NTM-PD greater than 6 months after their bronchiectasis diagnosis. While certainly some of these cases could have had pre-existing NTM-PD at the time of their bronchiectasis diagnosis, our sensitivity analysis still suggests a substantial risk of subsequent NTM-PD diagnosis in those with bronchiectasis.

While COPD is a known risk factor for NTM-PD [9], we found a lower incidence of NTM-PD among those bronchiectasis patients who had COPD, as compared to those lacking COPD. We suspect the strata of bronchiectasis patients lacking COPD were more likely those with bronchiectasis as their primary lung disorder, as opposed to those with COPD as a primary lung disorder with usually more mild findings of bronchiectasis [10]. This would explain the higher incidence we observed in this strata, as the risk of NTM-PD is known to be much higher in those with underlying bronchiectasis than those with underlying COPD as a primary lung disorder [9, 10].

A limitation of this analysis is the use of diagnostic codes for NTM-PD as they are about 50% sensitive [11]. The addition of NTM-PD therapy added some additional cases, but we still likely underestimated those who acquired NTM-PD. Strengths of this analysis include that Medicare data provides complete claims and demographic data, and these large datasets are ideally suited to study rare conditions such as bronchiectasis and NTM-PD. Medicare data includes the older population impacted by NTM-PD and bronchiectasis.

Our findings are consistent with underlying bronchiectasis as a strong risk factor in an older population in the USA for NTM-PD acquisition. Additional analysis of younger populations with bronchiectasis and evaluation of preventive strategies are required in order to better understand the relationship between NTM-PD and bronchiectasis.

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