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Early View

Research letter

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Prevalence, risk factors and prognosis of Non tuberculous mycobacteria infection among people with bronchiectasis: a population survey

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Introduction

The incidence of non- tuberculous mycobacteria (NTM) infection among people with bronchiectasis varies between different geographical areas and accordingly between different series[1,2]. Studies are largely based on bronchiectasis referral centers, which routinely screen for NTM in respiratory secretions. Therefore, the reported estimates of NTM prevalence in bronchiectasis may be exaggerated. Studies from bronchiectasis centers show conflicting results regarding risk factors for NTM: older age was found to increase risk in some but not other centers[1–4]. Due to the small numbers of patients in these studies, it is usually not possible to determine the effect of NTM infection on prognosis.

Utilizing the population registry of Israel's largest health maintenance organization[5], we aimed to determine the incidence, risk factors and prognosis of NTM infection among patients with bronchiectasis.

Methods

The database was searched for adults with bronchiectasis on January 1, 2010, excluding cystic fibrosis and Idiopathic Pulmonary Fibrosis. We searched for laboratory codes indicating NTM between January 2010 and December 2016. We defined three categories of NTM: 1. "Growth"- a single culture positive for any NTM; 2. "Colonization"- At least two cultures positive for the same NTM species; 3 "Treated"- either of the above categories, treated with three or more anti-mycobacterial drugs. Medication use was determined from pharmacy reports. Socioeconomic status (SES) was based on the SES score of the clinic neighborhood as defined by the Israeli Central Bureau of Statistics[6]. Mortality and hospitalizations during follow up (2010-2016) were compared between patients with and without NTM infection.

Multivariate Logistic Regression was used to identify the NTM risk factors. The Cox Time dependent model was used to identify prognostic factors that influence hospitalization and mortality.

Results

On 1/1/2010, the database included 2,710,432 adults. Of these, 6347 had a diagnosis of bronchiectasis (234:100,000). 6274 patients were without NTM infection prior to 1/1/2010. Of them only 1871 (30%) patients had mycobacterial cultures available. In the general population (without bronchiectasis) 1476 (0.055%) people had NTM from respiratory specimens during follow up. Among people with bronchiectasis (n=6274), 105 (1.7%) grew NTM during follow up. Only 30 cases (0.48%) had two or more cultures of the same NTM species, representing colonization. Treatment with a combination of three or more anti- mycobacterial drugs was found in 12 (0.19%) patients.

The incidence of NTM growth among all patients with bronchiectasis (n=6274) was estimated in four strata of age; 18-40, 40-60, 60-80, and >80 years. The corresponding incidence of NTM growth were 1.1%, 2.2%, 1.9%, and 0.9, respectively (P = 0.030). 50% of patients were 60-80 years old with a similar age distribution between patients with and without available mycobacterial cultures. Overall, 43% of patients with bronchiectasis in our study had emigrated from areas where Tuberculosis is common, specifically Africa and Eastern Europe. NTM incidence was 1.5% in immigrants from Africa and Eastern Europe and 1.8% in others (P = 0.355).

In bronchiectasis, the most common NTM species were *Mycobacterium simiae* (35 patients, 33%), Mycobacterium *avium- intracelulare* (MAI) (26, 25%), *M. fortuitum* (16, 15%) and *M. Abscessus* (11, 10.5%). Growth of *M. abscessus* and of *M. simiae* were significantly more common than in the general population (*abscessus*- 5.5%, p= 0.035; *simiae*- 23.5%, p= 0.023). Colonized patients had *M. simiae, Mycobacterium avium- intracelulare* (MAI) (30% each) and *M. abscessus* (27%). Patients that were treated for NTM infection had MAI (50%), *M. abscessus* (25%) and *M. kansasii* (25%).

In a multivariate logistic regression model that included 5737 bronchiectasis patients with complete information, young age, female sex, having never smoked, medium or high SES, glucocorticoid use, and antibiotic use were all independent risk factors for NTM growth. We repeated the model taking only the 1871 patients for whom mycobacterial cultures were available: non- smoking and medium-high SES remained significantly associated with NTM growth. We compared the 30 patients with colonization of NTM to the two other groups (patients with a single growthor no NTM growth). Younger age, female sex, and having been treated with antibiotics or prednisolone were significantly associated with colonization. A history of past smoking was significantly less common among patients with colonization than patients with a single NTM growth (P= 0.024, Table).

Over the follow up period, there were 1697 deaths and 3959 hospitalizations among 5737 patients with complete information. Growth of NTM was associated with a higher risk of mortality (adjusted HR= 1.56; 95% CI= 1.02-2.4, p=0.039) and hospitalizations (HR= 1.57 ; 95%CI, 1.05-2.34, p=0.029). Among the 30 patients with colonization of NTM, mortality was not increased compared to non-colonized (Adjusted HR 1.13 [0.47-2.75], p=0.784).

Discussion

In this study, based on a database analysis of over 6000 patients with bronchiectasis, we found that the incidence of NTM growth in bronchiectasis is considerably lower than previously reported: over 7 years of follow up, only 1.7% of the patients with bronchiectasis had detection of and NTM species

from respiratory infections, representing 5.6% positive cultures- slightly less than previous reports [1-4,7,8] . Less than 0.48% had colonization and only 0.19% were treated for NTM. An incidence of 1.7% may be an underestimation of the true incidence, since only 30% of patients had a mycobacterial culture sent. This figure may be a reflection of the practice (supported by guidelines) to send mycobacterial cultures only when there is a clinical suspicion of NTM pulmonary disease, rather than routine testing. Similarly to previously described in Israel[9] we found a high prevalence of *M. Simiae*, with only a minority of species considered pathogenic. Interestingly, we did not find any isolation of *M. Xenopi* in bronchiectasis, and only 27 (1.8%) in patients without bronchiectasis, unlike previously described results from Israel.

We couldn't determine how many of our patients filled ATS/IDSA criteria for NTM lung infection[10]. However, many of the strains in our population are not considered pathogenic or are resistant to antimicrobials[11], with *M. simiae* comprising 30% of the strains. Therefore, the decision to withhold treatment may have been justified.

A higher risk for NTM growth was found among patients from a high SES, never smoking and indices of disease severity, such as hospitalization and glucocorticoid and antibiotic treatment (Table). This association may reflect surveillance bias, as these patients may be subject to intensive follow up because of disease severity or increased health consciousness, leading to more frequent testing and detection of NTM. We achieved similar results when we repeated the analysis only in individuals with available mycobacterial cultures. Prior glucocorticoid and antibiotics use may increase the risk for NTM infection, respectively by immune compromise and selecting for resistant organisms.

We found that smoking was associated with a lower risk for NTM growth (28% past or present smokers vs. 36% among people without NTM growth), and even more so for colonization (16.7%, P= 0.024). A similar association was found previously in another bronchiectasis cohort [12], and has been reported in other granulomatous lung diseases such as sarcoidosis and hypersensitivity pneumonitis[13]. Inhibition of granuloma formation by smoking may possibly explain our finding[14]. Another factor associated with lower risk for NTM growth was low socioeconomic status (SES). A possible explanation is that smoking, more prevalent among people from a low SES, was not fully accounted for. Other factors associated with higher SES may also be important, possibly use of home water filtering systems.

In our analysis, younger age was associated with an elevated risk of NTM growth, with the highest prevalence in the 40-60 age group. Previous studies in bronchiectasis patients[4,12,15] ,were contradicting in the association of age and NTM growth.

Growth of NTM was associated with an increased risk of mortality (adjusted HR, 1.56, p=0.039) and hospitalizations (adjusted HR 1.57, p=0.029). In the 30 patients with colonization, mortality was not increased.

Our study has several limitations. The variables were based on electronic medical records and may be subject to inaccuracy or underreporting. We could not assess whether individuals with NTM fulfilled ATS/IDSA criteria for lung NTM infection[10]. We did not have data on radiological findings, lung function nor could calculate a bronchiectasis severity score, and we used three anti-mycobacterial drugs as a surrogate for NTM treatment. However, NTM lung disease in Israel is managed exclusively by pulmonologists, who are familiar with the NTM guidelines for diagnosis and treatment. Furthermore, the identification of NTM species is centralized by reference mycobacterial laboratories. In addition, this study included data from a large cohort of people with bronchiectasis and therefore could assess risk factors for NTM acquisition. Further research is required to explore the association of NTM and higher SES, younger age, and the negative association with smoking.

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Table: Demographic and clinical characteristics distribution according to NTM status (No NTM vs. single growth vs. colonization) and adjusted OR (95% CI) for the association with any NTM growth (composite of single growth and colonization)

	No NTM N=6169	**NTM- Single growth N=75**	**NTM Colonization N=30**	**P-value***	**Adjusted OR** (95% CI)**
Age Below 65	2542 (41.2)	40 (53.3)	16 (53.3)	0.044	**2.1 (1.4-3.10)**
Female N(%)	3324 (53.9)	52 (69.3)	21 (70.0)	0.006[a]	**1.66 (1.1-2.60)**
Ethnicity				0.512	
Jews N(%)	5472 (88.7)	69 (92.0)	28 (93.3)		Ref.
Arabs N(%)	697 (11.3)	6 (8.0)	2 (6.7)		0.60 (0.28-1.30)
SES				0.158	
Low N(%)	2141 (38.0)	19 (26.0)	7 (25.0)		Ref.
Medium N(%)	2333 (41.4)	36 (49.3)	13 (46.4)		**1.86 (1.12-3.10)**
High N(%)	1162 (20.6)	18 (24.7)	8 (28.6)		**1.83 (1.03-3.30)**
Macrolide treatment During 2009	1351 (21.9)	23 (30.7)	7 (23.3)	0.187	0.96 (0.61-1.50)
Any Antibiotic treatment during 2009	4331 (70.2)	65 (86.7)	26 (86.7)	0.001[a]	**2.50 (1.30-4.70)**
Prednisone treatment during 2009	1082 (17.5)	21 (28.0)	9 (30.0)	0.013[a]	**1.80 (1.15-2.85)**
Smoking (Current/past)	2261 (36.7)	21 (28.0)	5 (16.7)	0.024[b]	**0.60 (0.37-0.97)**
Any Hospitalization before 2010 N (%)	3311 (53.7)	40 (53.3)	20(66.7)	0.362	1.20 (0.78-1.80)

Risk assesment of acquiring NTM growth and colonization.

*Comparison between 3 groups

** Adjusted OR for any growth (composite of single growth and colonization)

[a] Significant difference after Bonferroni correction between No NTM and NTM single growth

[b] Significant difference after Bonferroni correction between NTM single growth and NTM colonization