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Short Communication

Epidemiology of nontuberculous mycobacteria (NTM) amongst individuals with cystic fibrosis (CF)

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Abstract

Background: Infection by nontuberculous mycobacteria (NTM) in patients with cystic fibrosis (CF) is often associated with significant morbidity. Limited, conflicting results are published regarding risk factors for pulmonary NTM disease. We analysed factors potentially associated with NTM in a large population of European patients with CF.
Methods: We investigated associations between presence of NTM and various factors for patients registered in the European Cystic Fibrosis Society Patient Registry.
Results: 374 (2.75%) of 13,593 patients studied had at least one positive NTM culture within the study year. Age- and FEV_1-adjusted odds of NTM infection was more than 2.5 times higher (95%CI: 1.79; 3.60) in patients infected by *Stenotrophomonas maltophilia* than in patients not infected ($p < 0.0001$), 2.36 times higher (95%CI: 1.80;3.08) in patients with ABPA than without ($p < 0.0001$), 1.79 times higher (95%CI: 1.34; 2.38) in patients who use bronchodilators than in patients who don't ($p < 0.0001$), 1.49 times higher (95%CI: 1.18; 1.89) in patients who use inhaled antibiotics than in patients who don't ($p = 0.001$), and 1.30 times higher (95%CI: 1.02; 1.66) in patients who use rhDNase than in patients who don't ($p = 0.032$).
Conclusions: NTM-positive cultures in individuals with CF are associated with distinct clinical variables. Improved data collection identifying risk factors for NTM infection will allow more focused screening strategies, and influence therapeutic choices and infection control measures in high-risk patients.

Keywords: Nontuberculous mycobacteria; Cystic fibrosis; Risk factors; Patient registry; Epidemiology

1. Introduction

Nontuberculous mycobacteria (NTM) represent a significant emerging threat in patients with CF. The limited studies examining NTM in CF to date have shown conflicting results with an increasing rate of infection with NTM shown in most (but not all) studied cohorts [1–3]. We currently do not understand the factors which may predispose to NTM infection in CF. Recently, a large US registry-based study reported potential risk factors for NTM using CFF data [4]. No such study has been undertaken in Europe.

Given the geographical variation in the prevalence of different NTM species between the US and Europe, the growing threat of NTM infection in both adult and paediatric CF patients, and the potential for person-to-person transmission, we undertook a population-based analysis of the factors associated with the isolation of NTM in a large population of European patients with

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CF using the European Cystic Fibrosis Society Patient Registry (ECFSPR) data.

2. Methods

The ECFSPR data collection methods have been described elsewhere in detail [5]. Briefly, the registry annually collects data from national CF registries and individual CF centres in Europe pertaining to individuals with CF and records information on the following: demographics, diagnosis, genotype, lung function, growth, complications, microbiology, transplant and therapy.

Further details regarding the definitions are outlined on the ECFSPR webpages [https://www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions] and in the 2008–2009 ECFSPR annual report, downloadable at https://www.ecfs.eu/files/webfm/webfiles/File/ecfs_registry/ECFSPR_Report0809_v32012.pdf.

We extracted data from the patients registered in ECFSPR in year 2009 (latest registry update at time of analysis). For the purposes of this cross-sectional study, to avoid patient and information selection bias, we selected data from countries that self-reported a good coverage (~90%) of their national CF population, and that had an acceptable level of missing information on isolation of NTM (<5%).

Further details regarding the methods are outlined in the Supplementary Material.

We used logistic regressions to investigate associations between the presence of NTM and age, sex, genotype, FEV_1, BMI, therapy, occurrence of infections and complications. We adjusted the estimates for the effect of country, to account for potentially different NTM screening and testing procedures, potential differences in provision of care, and data collection methods (such as sampling practices and time of FEV_1 measurements).

We built the final multivariable model, adding first the covariates that showed stronger evidence of an association with the presence of NTM at univariate analysis. We evaluated the impact of additional covariates through the computation of p-values and the observation of the change of the odds ratios of the covariates already in the model. We retained in the final model the covariates for which the p-value was <0.05.

3. Results

The prevalence of NTM reported by the ECFS Patient Registry for the year 2009 from each European country is shown in the Supplementary Material. We focused our analysis on patient data from France, Sweden and UK, which had a high coverage of their national CF population, an acceptable proportion of missing values for NTM, and that reported more than 2 cases of NTM during the study year. The main demographic and clinical characteristics of the study participants are summarised in Table 1.

Compared to NTM-negative patients, we found that NTM-positive patients were older, had lower BMI values, worse FEV_1, were more likely to be infected by *Pseudomonas aeruginosa* and by *Stenotrophomonas maltophilia*, were more likely to have experienced pneumothorax requiring chest drain, haemoptysis and liver disease, were more likely to make use of inhaled hypertonic saline, inhaled antibiotics, inhaled bronchodilators, oxygen therapy, inhaled rhDNase, macrolides, ursodeoxycholic acid and pancreatic enzymes.

3.1. Univariate models

When we formally tested these differences between NTM-positive and negative populations through logistic regression analysis (Table 2, we found a statistically significant association between presence of NTM and age ($p < 0.0001$). After adjusting for the effect of age (which would act as a confounder), there was evidence of an association between NTM and FEV_1 ($p < 0.0001$), BMI ($p = 0.0016$), inhaled hypertonic saline ($p = 0.0002$), inhaled antibiotics ($p < 0.0001$), inhaled bronchodilators ($p < 0.0001$), oxygen therapy ($p = 0.0099$), use of inhaled rhDNase ($p < 0.0001$), use of macrolides ($p < 0.0001$), use of ursodeoxycholic acid ($p < 0.0001$), use of pancreatic enzymes ($p = 0.0033$), *P. aeruginosa* colonisation ($p = 0.0218$), *S. maltophilia* ($p < 0.0001$), ABPA ($p < 0.0001$), liver disease ($p = 0.0001$), and haemoptysis ($p = 0.0124$).

3.2. Multivariable models

The following covariates were included in the final model, built on 9382 patients, 323 of whom had NTM: age, FEV_1, infection with *S. maltophilia*, presence of ABPA, use of bronchodilators, use of antibiotics and use of rhDnase.

As shown in Table 3, the odds of NTM infection was more than 2.5 times higher (95%CI: 1.79; 3.60) in patients infected by *S. maltophilia* than in patients not infected ($p < 0.0001$), 2.36 times higher (95%CI: 1.80; 3.08) in patients with ABPA than without ($p < 0.0001$), 1.79 times higher (95%CI: 1.34; 2.38) in patients who use bronchodilators than in patients who don't ($p < 0.0001$), 1.49 times higher (95%CI: 1.18; 1.89) in patients who use inhaled antibiotics than in patients who don't ($p = 0.001$), and 1.30 times higher (95%CI: 1.02; 1.66) in patients who use rhDNase than in patients who don't ($p = 0.032$). For each additional 10 years of age we estimate an increase of odds of infection of NTM by 17.5% (95%CI: 6.1; 30.2%, $p = 0.002$) and for each 10 percentage point increase in predicted FEV1 we estimate a decrease of odds of infection of NTM by 7.5% (95%CI: 3.0; 13.6%).

4. Discussion

This study represents the largest epidemiological analysis of NTM in individuals with CF from European countries for which there was evidence of unbiased reporting of NTM infection (France, Sweden and the UK) and has identified a number of clinical variables associated with NTM infection. There are, however, a number of important limitations of this study: its cross-sectional nature prevents identification of causal factors for NTM infection; the lack of species information about cultured NTM (as with previous US data [6] prevents sub-group analysis of MAC and MABSC infection, which are thought to infect different groups [7] and have distinct clinical outcomes [8]; a large number of European countries provided incomplete ECFSPR data on NTM preventing a larger, more