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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

Table 1
Descriptive statistics of demographic and clinical characteristics of population under study, by NTM group.

Covariate	Group		
	NTM = yes	NTM = no	All
Number of patients (%)	374 (2.7)	13,219 (97.3)	13,593
Sex: N (%) females	159 (42.5)	6279 (47.5)	6438 (47.4)
Age (years)			
Mean	24.7	19.0	19.2
Standard deviation	12.4	12.8	12.8
Median	21.8	17.4	17.6
Range	0.6–71.1	0.0–82.5	0.0–82.5
Adults (≥18 years): N (%)	264 (70.6)	6365 (48.2)	6629 (48.8)
Children (<18 years): N (%)	110 (29.4)	6854 (51.8)	6964 (51.2)
Genotype			
Number of patients undergone DNA analysis (%)	361 (96.5)	12654 (95.7)	13015 (95.7)
N (%) F508del/F508del	189 (52.3)	6284 (49.7)	6473 (49.7)
N (%) F508del/other	131 (36.3)	4968 (39.3)	5099 (39.2)
N (%) other/other	41 (11.4)	1402 (11.0)	1443 (11.1)
N (%) class I,II, III/I, II, III	242 (67.0)	8307 (65.6)	8549 (65.7)
N (%) Class I,II, III/IV, V	12 (3.3)	638 (5.0)	650 (5.0)
N (%) Class IV, V/IV, V	0 (0.0)	20 (0.2)	20 (0.1)
N (%) class undetermined	107 (29.7)	3689 (29.2)	3796 (29.2)
BMI			
Adults (≥18 years)			
BMI available for N (%)	256 (97.0)	5890 (92.5)	6146 (92.7)
N (%) <16.0 Kg/m^2	7 (2.7)	113 (1.9)	120 (2.0)
N (%) [16.0–17.0) Kg/m^2	9 (3.5)	203 (3.4)	212 (3.4)
N (%) [17.0–18.5) Kg/m^2	32 (12.5)	694 (11.8)	726 (11.8)
N (%) [18.5–25.0) Kg/m^2	174 (68.0)	4039 (68.6)	4213 (68.6)
N (%) [25.0–30.0) Kg/m^2	26 (10.2)	683 (11.6)	709 (11.5)
N (%) ≥ 30.0 Kg/m^2	8 (3.1)	158 (2.7)	166 (2.7)
Children (<18 years)			
BMI available for N (%)	101 (91.8)	5686 (82.6)	5787 (83.1)
N (%) < −2 SDS	2 (2.0)	75 (1.3)	77 (1.3)
N (%) −2; +2 SDS	99 (98.0)	5608 (98.6)	5707 (98.6)
N (%) > +2 SDS	0 (0.0)	3 (0.1)	3 (0.1)
FEV_1% of predicted			
N (%) patients ≥6 years	359 (96.0)	10971 (83.0)	11330 (83.4)
FEV_1% available for N (%)	341 (95.0)	9627 (87.7)	9968 (88.0)
N (%) <40% of predicted	82 (24.0%)	1417 (14.7%)	1499 (15.0%)
N (%) 40–80% of predicted	183 (53.7%)	4342 (45.1%)	4525 (45.4%)
N (%) >80% of predicted	76 (22.3%)	3868 (40.2%)	3944 (39.6%)
6–9 years: mean (SD)	65.8 (20.9)	89.5 (17.5)	89.4 (17.6)
10–14 years: mean (SD)	74.7 (22.6)	85.8 (19.3)	85.6 (19.4)
15–19 years: mean (SD)	63.0 (20.2)	73.3 (23.0)	72.8 (23.0)
20–24 years: mean (SD)	60.0 (24.2)	63.5 (24.2)	63.4 (24.2)
25–29 years: mean (SD)	56.3 (25.1)	58.8 (24.0)	58.7 (24.0)
30–34 years: mean (SD)	54.8 (17.7)	59.9 (24.2)	59.8 (24.1)
35–39 years: mean (SD)	53.8 (22.5)	58.7 (24.5)	58.5 (24.4)
40–44 years: mean (SD)	53.0 (26.9)	59.6 (26.3)	59.4 (26.3)
45+ years: mean (SD)	52.7 (24.0)	57.8 (24.7)	57.5 (24.7)
Infections: number of patients (%) with chronic infection by			
Pseudomonas aeruginosa	155 (41.4)	3859 (29.2)	4014 (29.5)
Stenotrophomonas maltophilia	54 (14.4)	570 (4.3)	624 (4.6)
Burkholderia cepacia complex	7 (1.9)	292 (2.2)	299 (2.2)
Complications: number of patients (%) with			
ABPA	96 (25.7)	1264 (9.6)	1360 (10.0)
Liver disease	61 (16.3)	1279 (9.7)	1340 (9.8)
Haemoptysis	21 (5.6)	343 (2.6)	364 (2.7)
Pneumothorax requiring chest drain	5 (1.3)	108 (0.8)	113 (0.8)
Malignancy	0 (0.0)	34 (0.3)	34 (0.3)
Therapy: number of patients (%) using			
Insulin	61 (16.3)	1697 (12.8)	1758 (12.9)
Inhaled hypertonic saline	45 (12.0)	832 (6.3)	877 (6.4)
Inhaled antibiotic	191 (51.1)	4458 (33.7)	4649 (34.2)

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Table 1 (*continued*)

Covariate	Group		
	NTM = yes	NTM = no	All
Inhaled bronchodilators	277 (74.1)	6676 (50.5)	6953 (51.2)
Oxygen therapy	40 (10.7)	739 (5.6)	779 (5.7)
Inhaled rhDNase	216 (57.7)	5165 (39.1)	5381 (39.6)
Macrolides	198 (52.9)	4971 (37.6)	5169 (38.0)
Ursodeoxycholic acid	121 (32.3)	3123 (23.6)	3244 (23.9)
Pancreatic enzymes	320 (85.6)	10818 (81.8)	11138 (81.9)

comprehensive analysis of national variations in NTM infection; and finally the ECFSPR fails to capture the number of samples sent for NTM culture (as well as for the other infections) and therefore preventing an evaluation of the sampled cohort and hence analysis of the true prevalence of NTM in individuals with CF. Furthermore, not all the European countries followed the ECFSPR guidelines relating to the definition of chronic infections and the timing of FEV_1 measurement. However, the impact of the choice of any specific value from a set of values over a year has been shown to be small [9]. To overcome the problem differences artificially induced by the study design (screening and reporting of NTM infections, data collection practices, etc.)we adjusted our estimates by introducing the country as a factor in the models.

Isolation of *S. maltophilia* was associated with the presence of NTM, echoing a recent US CFF registry-based study [4], potentially due to the fact that both are resistant bacteria that may thrive under conditions of high antibiotic usage. We also observed a negative association of NTM with chronic *P. aeruginosa* infection, similar to a recent US study [4].

The relationship between NTM-positive cultures and macrolide use is unclear in our data. Univariate analysis suggested a potential association between NTM-positive cultures and macrolide use in keeping with a previous small, single-centre study [10] suggesting that chronic azithromycin use might predispose to MABSC infection by blocking autophagic intracellular killing. However, multivariate analysis of our data failed to demonstrate an association between NTM-positive cultures and macrolide use. Recent data from a US population-based study [4] and a small case–control study from France [7] suggest that the use of maintenance macrolide therapy may be associated with a decreased likelihood of NTM. Given the multi-collinearity of macrolide usage and chronic pseudomonas infection in our dataset, we are unable to estimate the effect of

Table 2
Results from univariate logistic regressions: effect of single covariates on the odds of being infected by NTM.

Covariate	OR	95%CI	p-Value
Sex (male vs female)	1.223	0.994; 1.506	0.057
Age on 31/12/2009 or age at death if died during study year (years)	1.030	1.023; 1.038	<0.0001
F508del genotype			0.515
F508del heterozygote vs F508del homozygote	0.877	0.699; 1.099	
No F508del allele vs F508del homozygote	0.972	0.690; 1.370	
Mutation class			0.540
class I,II,III/I,II,III vs class undetermined	1.009	0.807; 1.262	
class I,II,III/IV, V vs class undetermined	0.652	0.358; 1.187	
class IV,V/IV,V vs class undetermined	<0.001	<0.001; >999.999	
FEV_1% of predicted [a]	0.986	0.981; 0.990	<0.0001
BMI z-score [a]	0.872	0.800; 0.949	0.002
Use of inhaled hypertonic saline during study year [a] (Yes vs no)	1.825	1.323; 2.518	0.0002
Use of inhaled antibiotic during study year [a] (Yes vs no)	1.934	1.568; 2.386	<0.0001
Use of inhaled bronchodilators during study year [a] (Yes vs no)	2.484	1.962; 3.146	<0.0001
Use of Oxygen therapy during study year [a] (Yes vs no)	1.570	1.114; 2.211	0.010
Use of rhDNase during study year [a] (Yes vs no)	2.072	1.682; 2.553	<0.0001
Use of macrolide during study year [a] (Yes vs no)	1.542	1.248; 1.906	<0.0001
Use of ursodeoxycholic acid during study year [a] (Yes vs no)	1.595	1.273; 1.997	<0.0001
Use of pancreatic enzymes during study year [a] (Yes vs no)	1.652	1.182; 2.309	0.003
Chronic infection by *Pseudomonas aeruginosa* [a] (Yes vs no)	1.299	1.039; 1.624	0.022
Chronic infection by *Staphylococcus aureus* [a] (Yes vs no)	1.153	0.820; 1.620	0.412
Chronic infection by Burkholderia cepacia complex [a] (Yes vs no)	0.702	0.329; 1.498	0.360
Infection by *Stenotrophomonas maltophilia* [a] (Yes vs no)	3.576	2.640; 4.843	<0.0001
Presence of ABPA during study year [a] (Yes vs no)	3.118	2.453; 3.965	<0.0001
Daily use of insulin during study year [a] (Yes vs no)	0.973	0.731; 1.295	0.850
Occurrence of Pneumothorax requiring chest drain during study year [a] (Yes vs no)	1.418	0.574; 3.501	0.449
Presence of liver disease during study year [a] (Yes vs no)	1.741	1.314; 2.305	0.0001
Occurrence of haemoptysis major over 250 ml during study year [a] (Yes vs no)	1.793	1.135; 2.833	0.012
Occurrence of malignancy during study year [a] (Yes vs no)	<0.001	<0.001; >999.999	0.973

[a] Effect adjusted by age: age was included as additional covariate in the model.

Table 3
Results from multivariable logistic regressions: effect on odds of NTM infection of age, FEV_1, infection with *Stenotrophomonas maltophilia*, presence of ABPA, use of bronchodilators, use of antibiotics, and use of rhDnase. The estimates are adjusted by the effect of country. The model was built using data from 9382 CF patients.

Covariate	Odds ratio	95% CI		p-Value
Stenotrophomonas maltophilia (Yes vs no)	2.54	1.79	3.60	<0.0001
ABPA this year (Yes vs no)	2.36	1.80	3.08	<0.0001
Inhaled bronchodilators this year (Yes vs no)	1.79	1.34	2.38	<0.0001
Inhaled antibiotic this year (Yes vs no)	1.49	1.18	1.89	0.001
Use of rhDNase this year (Yes vs no)	1.30	1.02	1.66	0.032
Age (decade)	1.17	1.06	1.30	0.002
FEV_1% of predicted, unit expressed as change of 10 percent points.	0.93	0.88	0.97	0.003

these factors on NTM infection. Further information regarding the treatment of these variables in the regression model is contained in the Supplementary Material. Large, longitudinal studies will be required to definitively determine whether macrolides may predispose to NTM infection in individuals with CF.

We also found an association between ABPA and NTM-positive cultures which has been reported by some [11] but not other studies [7,10,12]; inconsistencies potentially due to differences in case definitions for ABPA and/or variations in oral steroid usage. While there are a number of plausible reasons for a causal relationship between ABPA and NTM (including ABPA-associated immunomodulation [10,13,14] and/or reduced airway clearance), our data highlights the importance of heightened vigilance for NTM infection in CF patients with ABPA.

Our study shows a relationship between the use of inhaled bronchodilators, inhaled antibiotics and, to a lesser extent, inhaled rhDNAse with NTM isolation in patients with CF. It has been suggested [15,16] that rhDNAase may promote infection with MABSC by providing degraded DNA as a mycobacterial nutrient. Use of inhaled corticosteroids has been associated with an increased risk of pulmonary NTM disease in patients with COPD [17] and asthma [18]. Previous studies in CF populations to date have not demonstrated a similar effect [7,19].

In summary, our study identifies a number of potential risk factors for the acquisition of NTM in CF that will require further study. Understanding these risk factors is key to reducing the incidence of NTM infection and will allow a more focused screening strategy for NTM, and could influence therapeutic choices and infection control measures in these high-risk patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2016.03.002.

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