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Original Article

Comparing the harmful effects of nontuberculous mycobacteria and Gram negative bacteria on lung function in patients with cystic fibrosis☆

Tavs Qvist [a,1], David Taylor-Robinson [b,*,1], Elisabeth Waldmann [c], Hanne Vebert Olesen [d], Christine Rønne Hansen [e], Inger Hee Mathiesen [a], Niels Høiby [f], Terese L. Katzenstein [a], Rosalind L. Smyth [g], Peter J. Diggle [h], Tania Pressler [a]

[a] *Copenhagen Cystic Fibrosis Center, Department of Infectious Diseases, Rigshospitalet, Copenhagen University, Denmark*
[b] *Department of Public Health and Policy, University of Liverpool, Liverpool, UK*
[c] *Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany*
[d] *Aarhus Cystic Fibrosis Center, Department of Pediatrics, University Hospital Skejby, Aarhus, Denmark*
[e] *Copenhagen Cystic Fibrosis Center, Department of Pediatrics, Rigshospitalet, Copenhagen University, Denmark*
[f] *Copenhagen Cystic Fibrosis Center, Department of Clinical Microbiology, Rigshospitalet, Copenhagen University, Denmark*
[g] *Institute of Child Health, University College London, London, UK*
[h] *Faculty of Medicine, Lancaster University, Lancaster, UK*

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Abstract

Background: To better understand the relative effects of infection with nontuberculous mycobacteria and Gram negative bacteria on lung function decline in cystic fibrosis, we assessed the impact of each infection in a Danish setting.
Methods: Longitudinal registry study of 432 patients with cystic fibrosis contributing 53,771 lung function measures between 1974 and 2014. We used a mixed effects model with longitudinally structured correlation, while adjusting for clinically important covariates.
Results: Infections with a significant impact on rate of decline in %FEV1 were *Mycobacterium abscessus* complex with −2.22% points per year (95% CI −3.21 to −1.23), *Burkholderia cepacia* complex −1.95% (95% CI −2.51 to −1.39), *Achromobacter xylosoxidans* −1.55% (95% CI −2.21 to −0.90), and *Pseudomonas aeruginosa* −0.95% (95% CI −1.24 to −0.66). Clearing *M. abscessus* complex was associated with a change to a slower decline, similar in magnitude to the pre-infection slope.
Conclusions: In a national population we have demonstrated the impact on lung function of each chronic CF pathogen. *M. abscessus* complex was associated with the worst impact on lung function. Eradication of *M. abscessus* complex may significantly improve lung function.

Keywords: Lung function; Abscessus; NTM; Gram negative; CF

Abbreviations: ATS, American Thoracic Society; CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; CI, confidence interval; %FEV1, forced expiratory volume in 1 s expressed as % of predicted; IDSA, Infectious Disease Society of America; MABSC, *Mycobacterium abscessus* complex; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria.

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* Corresponding author at: Department of Public Health and Policy, Whelan Building, University of Liverpool, Liverpool, UK.
E-mail addresses: tavs.qvist@gmail.com (T. Qvist), david.taylor-robinson@liverpool.ac.uk (D. Taylor-Robinson), elisabeth.waldmann@fau.de (E. Waldmann), hvo@dadlnet.dk (H.V. Olesen), christunte@dadlnet.dk (C.R. Hansen), ihm@dadlnet.dk (I.H. Mathiesen), hoibyniels@gmail.com (N. Høiby), terese.katzenstein@regionh.dk (T.L. Katzenstein), rosalind.smyth@ucl.ac.uk (R.L. Smyth), p.diggle@lancaster.ac.uk (P.J. Diggle), tania.pressler@gmail.com (T. Pressler).
[1] Contributed equally.

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1. Introduction

The natural history of CF lung disease is characterized by chronic progression with intermittent episodes of acute worsening of symptoms, termed pulmonary exacerbations, often precipitated by bacterial infections, which become established within viscid airway secretions. Understanding the distinct impact of chronic infections in cystic fibrosis (CF) is important, because lung function decline takes place in a setting of multiple competing pathogens. Prioritizing treatment starting with the most serious threat to patients' health is a central challenge for clinicians. While the impact of major Gram negative infections have previously been reported [1,2], there are limited data from population level studies comparing the relative influence of the major bacterial pathogens.

The principle of always using early, aggressive treatment aimed at eradication of both Gram positive and negative infection has been in use since 1976 in Denmark [3,4]. As a consequence chronic persistent *Staphyloccocus aureus* infection is infrequently seen [5]. Methicillin-resistant *S. aureus* is rare in Denmark in general and almost non-existent among patients with CF [5].

If eradication therapy for Gram negative bacteria fails, elective 2-week courses of intravenous chemotherapy are administered at regular intervals to pre-empt exacerbations and maintain lung function. Since 1987 inhaled antibiotics have been a part of the standard treatment of chronic infection with subsequent additions of continuous dornase alpha and azithromycin treatment, when these treatments became available. These principles have been employed for infection due to *Pseudomonas aeruginosa*, *Achromobacter xylosoxidans* and *Burkholderia cepacia* complex, which have all been described to be associated with worse outcomes, including survival, lung function, and nutritional status [1,6–9]. The significance of chronic infection with *Stenotrophomonas maltophilia* and nontuberculous mycobacteria (NTM) is less clear. Except in rare cases, *S. maltophilia* is not treated in Denmark [10], while NTM is subject to intensive treatment following guidelines from the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA)'s consensus documents [11]. Three previous studies of clinical outcomes following NTM have shown, respectively, no effect, significant effect or a calamitous effect on expected forced expiratory volume in 1 s (%FEV1) [12–14]. Understanding the significance of NTM on lung function in patients with cystic fibrosis (CF) is important, given the intensive therapeutic regimen required to clear infection, and associated side effects [11,15].

The aim of the study was to assess and contrast the impacts of chronic Gram negative infections and NTM on lung function in patients with CF. *Aspergillus* infection and Gram positive bacterial infection were not included in this dataset due to inherent differences in how chronic infection was defined and registered for these pathogens.

2. Methods

We undertook a longitudinal analysis of lung function in Danish patients with CF. All patients born from 1974 onwards were included if seen at the Copenhagen CF Center; patients seen at the other Danish CF center in Aarhus, were included from 2002. The pre-1974 birth cohorts were excluded to reduce the influence of survivor bias as previously described in this dataset [8]. Post-transplantation data were likewise excluded. Further methodological details are available in the online appendix.

2.1. Setting

Throughout the study period from 1974 to August 2014, patients attending the two Danish CF Centers were seen routinely every month in the outpatient clinic, for evaluation of clinical status, pulmonary function, and microbiology of lower respiratory tract secretions. Pulmonary function tests were performed according to international recommendations [16], measuring FEV1, expressed as a percentage of predicted values for sex and height using reference equations from Wang or Hankinson [17,18].

The hypothesis we wanted to test was that onset of infection with *Mycobacterium abscessus* complex (MABSC) and *Mycobacterium avium* complex (MAC) would lead to deterioration of lung function as previously shown with *P. aeruginosa*, *A. xylosoxidans*, *B. cepacia* complex and *S. maltophilia*. The primary outcome of interest in the statistical model was the change in slope of %FEV1 at the first time point, at which, individuals transitioned to fulfill the definition of chronic infection. Chronic Gram negative infection was defined according to modified Leeds criteria (more than 50% positive culture samples during a year). In Copenhagen, specific precipitating antibodies were also used to support the definition of chronic infection as previously described [4,19,20]. For NTM, the term chronic was not used, but we distinguished between patients who fulfilled the ATS/IDSA's criteria for NTM pulmonary disease [11], and those who did not. Onset of NTM infection was defined as the date of first recorded positive NTM culture. Clearing infection was defined as consistent culture negativity in >4 NTM cultures over a minimum of 12 months following cessation of NTM treatment. Throughout the period, patients were screened routinely for NTM during bronchoalveolar lavages and when clinically indicated. Between 1987 and 1988 and again from 2011 onward, all patients with CF in Copenhagen were also screened annually for NTM with mycobacterial culture.

2.2. Statistical analysis

We developed a longitudinal model for the data using a previously published approach [8,9]. In brief, we developed a multivariate longitudinal model to assess the association between onset (for all infections) and offset of infection (in the case of MABSC), and slope of lung function trajectory, while adjusting for birth cohort, genotype (coded as the number of delta F508 alleles (0, 1 or 2)); pancreatic insufficiency (PI) (coded 0 or 1 as a baseline covariate); and CF related diabetes (CFRD) diagnosed using previously published criteria (coded 0 or 1 as a time-varying covariate) [21]. The final model assumed a linear function for the population-averaged time-trend, though we explored non-linear approaches, which did not improve