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

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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.

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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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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 Staphylococcus 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 [6]. There have been a number of randomized controlled trials comparing the relative influence of the major bacterial pathogens.

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. Methods

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...
model fit (Appendix). The longitudinally structured correlation was modeled as an exponentially decaying function of time difference (Appendix) [8]. This approach provides a more realistic estimate of the %FEV1-trend of patients with chronic lung disease by taking into account the imprecision and correlation in repeated measurements on the same individual over time [21]. We assessed the influence of each infection individually first, and then in a mutually adjusted model containing all of the infections. We further assessed the effect of co-infection by adding interaction terms between the infections to the model. We estimated model parameters by maximum likelihood, using generalized likelihood ratio statistics to compare nested models when building the final multivariable model and the Akaike information criterion (AIC) to compare non-nested models (when testing for the significance of infection interaction terms); and Wald statistics to test hypotheses about model parameters [22]. We visualized the model parameters of interest by plotting population averaged %FEV1 trajectories with other model parameters held constant. As a robustness test we repeated the analysis dropping the earliest birth cohort due to the potential for survivor effects in the earlier birth cohorts. A level of 0.05 was set for statistical significance. R version 3.1.1 was used for the analysis (http://www.R-project.org).

2.3. Ethical considerations

The study was approved by the Danish Data Protection Agency (file no. 2008-41-2682).

3. Results

3.1. Population characteristics

The dataset contained 53,771 lung function measures on 432 patients who visited the Danish CF centers between 1974 and 2014. The median number of %FEV1 measures per person was 100 (range 1–530). The median follow-up period was 12.3 years (range 0–35.5), with a total of 9250 person-years of follow-up (see Appendix for further details). Seventy-six patients were followed for more than 30 years. The baseline characteristics of the population, stratified by birth cohort are shown in Table 1. Genotype and CFRD were not significant in the final multivariable population, stratified by birth cohort are shown in Table 1.

Table 1 Characteristics of Danish cystic fibrosis patients by birth cohort.

| Year       | Cohort | 1974 n (%) | 1984 n (%) | 1994 n (%) | 2004 n (%) | Total n (%) |
|------------|--------|------------|------------|------------|------------|-------------|
| Female     |        | 120 (27.8) | 133 (30.8) | 123 (28.5) | 56 (13)    | 432 (100)   |
| Pancreatic insufficiency | 112 (93.3) | 123 (92.5) | 120 (97.6) | 52 (92.9)  | 467 (94.2) |
| P. aeruginosa | 82 (68.3) | 34 (25.6)  | 22 (17.9)  | 3 (5.4)    | 141 (32.6) |
| S. maltophilia | 14 (11.7) | 22 (16.5)  | 21 (17.1)  | 5 (8.9)    | 62 (14.4)  |
| MABSC | 10 (8.3) | 22 (16.5)  | 9 (7.3)    | 3 (5.4)    | 44 (10.2)  |
| MAC | 5 (4.2) | 5 (3.8)    | 4 (3.3)    | 0 (0)      | 14 (3.2)   |
| A. xylosoxidans | 7 (5.8) | 31 (23.3)  | 1 (0.8)    | 1 (1.8)    | 40 (9.3)   |
| B. cepacia complex | 22 (18.3) | 13 (9.8)   | 2 (1.6)    | 0 (0)      | 37 (8.6)   |

3.2. Chronic infections

P. aeruginosa was the most common infection, followed by S. maltophilia, A. xylosoxidans and B. cepacia complex. Eighty-six (20%) patients developed two chronic infections (Table 2). Forty-four patients were culture positive for MABSC at least once; 14 patients had MAC and two had both MABSC and MAC infection. NTM patients contributed a total of 251 NTM positive person years to the study with a mean NTM positive follow-up time of 7.6 years. Thirty-nine (70%) patients cleared their NTM infection.

3.3. Effect of infections on lung function

With the exception of MAC, onset of all infections was associated with a significant acceleration in %FEV1 decline. On the basis of the point estimates, after adjustment for demographic, genetic and clinical factors, MABSC had the largest effect on lung function; −2.22 percentage points per annum (95% CI −3.21 to −1.23), followed by the B. cepacia complex −1.95 (95% CI −2.51 to −1.39), A. xylosoxidans −1.55 (95% CI −2.21 to −0.90), P. aeruginosa −0.95 (95% CI −1.24 to −0.66), and S. maltophilia −0.67 (95% CI −1.21 to −0.13) (Fig. 1). An overall Wald test confirmed that there were general significant differences between the effect sizes of the six infections (p < 0.001). The effect of multiple infections was checked by adding interactions between the infections to the model in cases where there were more than 10 people with co-infection (see Table 2). None of the interaction terms were significant or improved the model AIC.

Projecting the trend of the negative change in lung function for each CF pathogen into estimated time to the development of end stage lung disease, Fig. 2 illustrates the clinical consequence of each chronic infection. Thus, for a patient born in 1994 and infected at age 20, all other things being equal, end stage lung disease will occur after 13.6, 14.7, 16.8, 21.3, 24.4 and 35.6 years for MABSC, B. cepacia complex, A. xylosoxidans, P. aeruginosa, S. maltophilia and MAC respectively.

3.4. MABSC and lung function decline

Onset of MABSC was associated with the steepest decline in lung function decline, but clearance of the infection was associated with a change to a slower decline, similar in magnitude to the pre-infection decline (Fig. 1 and Fig. 3).

3.5. Robustness tests

Repeating the analysis only on data from patients born after 1984 and patients who fulfilled the ATS/IDSA criteria did not markedly change the results. Tests of the model fit are reported in the appendix.

4. Discussion

This is the first population level study to simultaneously compare the effects of different infections on the longitudinal...
rate of decline of lung function in CF. The strength of this analysis is the visit frequency of examinations (every month) and long period of follow-up in a complete national population, facilitating precise estimation of the time of onset of infection. Furthermore, the frequency of measures of the %FEV1 dataset allowed a more sophisticated statistical model to be used, which leads to more robust estimation of the rate of lung function decline [8]. The order of the negative effects on lung function was (worst to best): MABSC, *B. cepacia* complex, *A. xylosoxidans*, *P. aeruginosa*, and *S. maltophilia*.

### 4.1. NTM and lung function decline

With 21 years of follow-up of patients with NTM, this study provides strong evidence for the effects of MABSC and MAC on lung function in CF. MABSC demonstrated an effect of −2.2% of excess lung function decline per year; in contrast MAC infection had no significant effect. Previous studies have confirmed that MABSC is more virulent than MAC in patients with CF [11,23,24], but only three studies have looked at effects on lung function decline in CF. In 2003, Olivier et al. [12] showed that 18 patients with CF and ATS/IDSA defined NTM disease did not have a significantly accelerated lung function decline over a 15-month period. They suggested that a longer observation time might reveal a difference. In 2010, Esther et al. [13] examined longitudinal data from 23 patients with MABSC and found an excess lung function decline of −0.78% per year. Martiniano et al. [14] followed 70 MAC and 24 MABSC cases for three years after NTM infection and found excess annual rates of decline of −4.1% for those who fulfilled ATS/IDSA criteria, and −1.6% per year for those with only one positive culture. The authors did not distinguish between the effects of MABSC and MAC. In our analysis we did differentiate between the two species, but interestingly could not find an isolated effect of fulfilling ATS/IDSA criteria for NTM pulmonary disease. This could be due to an underestimation of patients who fulfilled the ATS/IDSA microbiological criteria, either from the early part of the cohort, where patients were cultured less frequently or due to the increase in MABSC cases seen in the last year of the study, where some new cases with clinical deterioration, did not have sufficient time to fulfill the criteria. Scandinavian NTM outcomes, including clearance rates have been published recently [25], with approximately half of ATS/IDSA defined NTM infected patients achieving culture negativity, typically, but not exclusively, following extensive treatment. Patients with MABSC were more likely to develop end stage lung

![Fig. 1. Change in the rate of decline of lung function (%FEV1) following onset of each infection and clearance of nontuberculous mycobacterial infection. The point sizes are drawn proportional to the precision of the estimates.](image-url)

![Fig. 2. Effect on lung function of chronic infection from onset to end stage lung disease in Danish cystic fibrosis patients. The figure visualizes the impact of onset of chronic infections by plotting population averaged %FEV1 trajectories before and after onset of infection with other model parameters held constant. Thus for a patient born in 1994 and infected at age 20, all other things being equal, end stage lung disease will occur after 13.6, 14.7, 16.8, 21.3, 24.4 and 35.6 years for MABSC, *B. cepacia* complex, *A. xylosoxidans*, *P. aeruginosa*, *S. maltophilia* and MAC respectively. Footnote: Trajectories plotted and held constant for a person born in the 1994–2004 birth cohort, mutually adjusted for other co-variates in the model, with onset of infection occurring at age 20.](image-url)
disease and the clinical significance of a first positive NTM culture was high, with almost 3 out of 4 eventually progressing from a first positive culture to a second [25].

4.2. Effect of clearing MABSC

The observed significant slower decline in lung function following MABSC clearance (1.9% improvement per year) was similar to the effect size of acquisition (−2.2% per year). To our knowledge, this is the first study to suggest that excessive loss of lung function may be mitigated by MABSC clearance and our observation of two entirely opposite effects after onset and clearance of disease give further weight to the notion of a causal association between MABSC infection and lung function decline [26].

4.3. Gram negative infection

The observed influence of the different Gram negative infections on lung function decline is not surprisingly in accordance with previous independent analyses from the Danish CF population [10,27–29]. Apart from A. xylosoxidans, the results are also in accordance with reports from other countries, which ascribes B. cepacia complex the worst role, albeit with some inter-species variation [30], followed by P. aeruginosa, for which there is a larger body of evidence [2,31] and finally S. maltophilia, which is not considered to be a serious cause of lung function decline [32,33], although this perception has been challenged [34]. A. xylosoxidans has been reported to have either no impact on lung function [35], or an effect indistinguishable from that of P. aeruginosa [36]. We did not demonstrate any interaction between infections in terms of their effects on lung functions, but this finding may reflect insufficient numbers to detect such effects. The omission of chronic Gram positive bacteria and Aspergillus infection was based on respectively very low prevalence and difficulties in comparing criteria for chronicity. The issue of whether the appearance of NTM in CF is the cause of, or alternatively the consequence of, deteriorating lung function is a key question. The reverse effect in lung function we observed following clearance of MABSC is compelling evidence that it is indeed the mycobacteria causing the deterioration and not the other way around. Limitations in the study are the retrospective design and the risk of ascertainment bias which could underestimate the mitigating effect of asymptomatic MABSC on the overall MABSC effect. Confounding independent of the variables we adjust for can likewise not be ruled out. Differences in how NTM infection and Gram negative infection are defined and screened for, can be expected to be built into any CF study since disease criteria and screening recommendations are dissimilar. Our robustness testing however suggested these differences were not important, as the same effect of MABSC was seen in children infected late in the period and independently of fulfilling ATS/IDSA criteria. The influence of survivor bias on lung function estimates in the earlier birth cohorts is a common problem in datasets of this type [37]. We handled this by excluding patients born before 1974 [8], where treatment regimens changed frequently. Repeating the analysis using only data from more recent cohorts did not alter the results. Furthermore, fitting the mixed effects longitudinal model by maximum likelihood implicitly takes this drop out into account and generates the parameter estimates that one would expect to see if dropout had not occurred [38,39].

4.4. Conclusions

In summary, we have demonstrated the marked effect on lung function of each Gram negative CF pathogen and NTM, allowing for the first time, to compare the infections in degrees of severity. We have shown how MABSC has an important negative effect on lung function, whereas we did not detect a significant effect for MAC infection. We observed that clearing MABSC may restore lung function decline to its previous slope, pointing to the important role of eradication therapy in cystic fibrosis.

Conflict of interest

DTR, EW and PD received funding from the Medical Research Council.

Contributions

Guarantors: DTR, TQ;
Conception and design: DTR, TQ, TP, RLS;
Data collection: HVO, IHM, CRH, TLK, NH;
Analysis and interpretation: DTR, EW, PJD, TQ; and
Drafting the manuscript for important intellectual content: TQ, DTR, EW, HVO, CRH, IHM, NH, TLK, RLS, PJD, TP.
Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2015.09.007.

References

[1] Konstan MW, Wagener JS, Vanlander DR, Pasta DJ, Yegin A, Rasouliyani L, et al. Risk factors for rate of decline in FEV1 in adults with cystic fibrosis. J Cyst Fibros 2012;11:405–11.
[2] Kerem E, Viviani L, Zolin A, MacNeill S, Hatzigourou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J 2014;43:125–33.
[3] Koch C, Hoiby N. Cystic fibrosis. 7. Management of cystic fibrosis in different countries. Cyst Fibros Copenhagen Thorax 1991;46:385–6 [discussion 389–90].
[4] Koch C, Hoiby N. Pathogenesis of cystic fibrosis. Lancet 1993;341:1065–9.
[5] Dalbøge CS, Pressler T, Hoiby N, Nielsen KG, Johansen HK. A cohort study of the Copenhagen CF Centre eradication strategy against Staphylococcus aureus in patients with CF. J Cyst Fibros 2013;12:42–8.
[6] Kosorok MR, Zeng L, West SE, Rock MJ, Splaingard ML, Laxova A, et al. Acceleration of lung disease in children with cystic fibrosis after Pseudomonas aeruginosa acquisition. Pediatr Pulmonol 2001;32:277–87.
[7] Emerson J, Rosenfeld K, McNamara S, Ramsey B, Gibson RL, Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol 2002;34:91–100.
[8] Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen HV, Pressler T, Smyth RL, et al. Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study. Thorax 2012;67:860–6.
[9] Taylor-Robinson DC, Smyth RL, Diggle PJ, Whitehead M. The effect of social deprivation on clinical outcomes and the use of treatments in the UK cystic fibrosis population: a longitudinal study. Lancet Respir Med 2013;1:121–8.
[10] Dalbøge CS, Hansen CR, Pressler T, Hoiby N, Johansen HK. Chronic pulmonary infection with Stenotrophomonas maltophilia and lung function in patients with cystic fibrosis. J Cyst Fibros 2011;10:318–25.
[11] Griffith DE, Aksamit T, Brown-Elliott B a, Catanarzo A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367–416.
[12] Olivier KN, Weber DJ, Lee J-HH, Handler A, Tudor G, Molina PL, et al. Nontuberculous mycobacteria. II: nested-cohort study of impact on cystic fibrosis lung disease. Am J Respir Crit Care Med 2003;167:835–40.
[13] Esther Jr CR, Esserman DA, Gilligan P, Kerr A, Noone PG, Esther CR. Chronic Mycobacterium abscessus infection and lung function decline in cystic fibrosis. J Cyst Fibros 2010;9:117–23.
[14] Martiniano SL, Sontag MK, Daley CL, Nick JA, Sagel SD. Clinical significance of a first positive nontuberculous mycobacteria culture in cystic fibrosis. Am Am Thorae Soc 2014;11:36–44.
[15] Nessar R, Cambau E, Reyart JM, Murray A, Ciguel B. Mycobacterium abscessus: a new antibiotic nightmare. J Antimicrob Chemother 2012;67:810–8.
[16] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38.
[17] Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15:75–88.
[18] Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–87.
[19] Hoiby N. Pseudomonas aeruginosa infection in cystic fibrosis. Diagnostic and prognostic significance of pseudomonas aeruginosa precipitins determined by means of crossed immunoelectrophoresis. A survey. Acta Pathol Microbiol Scand Suppl 1977;1–96.
[20] Pressler T, Bohmova C, Conway S, Dumcius S, Hjelte L, Hoiby N, et al. Chronic Pseudomonas aeruginosa infection definition: EuroCareCF Working Group report. J Cyst Fibros 2011;10(Suppl. 2):S75–8.
[21] Pincikova T, Nilsson K, Moen IE, Fluge G, Hollsing A, Knudsen PK, et al. Vitamin D deficiency as a risk factor for cystic fibrosis-related diabetes in the Scandinavian Cystic Fibrosis Nutritional Study. Diabetologia 2011;54:3007–15.
[22] Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963–74.
[23] Leung JM, Olivier KN. Nontuberculous mycobacteria: the changing epidemiology and treatment challenges in cystic fibrosis. Curr Opin Pulm Med 2013;19:662–9.
[24] Catherinot E, Roux AL, Vibet MA, Bellis G, Ravilly S, Lennonnier L, et al. Mycobacterium avium and Mycobacterium abscessus complex target distinct cystic fibrosis patient subpopulations. J Cyst Fibros 2013;12:74–80.
[25] Qvist T, Gilljam M, Jönsson B, Taylor-Robinson D, Jensen-Fang S, Wang M, et al. Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia. J Cyst Fibros 2015;14:46–52.
[26] HILL AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
[27] Rønne Hansen C, Pressler T, Hoiby N, Gormsen M. Chronic infection with Achromobacter xylosoxidans in cystic fibrosis patients; a retrospective case control study. J Cyst Fibros 2006;5:245–51.
[28] Hansen CR, Pressler T, Nielsen KG, Jensen PØ, Bjamsholt T, Hoiby N. Inflammation in Achromobacter xylosoxidans infected cystic fibrosis patients. J Cyst Fibros 2010;9:51–8.
[29] Hansen CR, Pressler T, Koch C, Hoiby N. Long-term azitromycin treatment of cystic fibrosis patients with chronic Pseudomonas aeruginosa infection; an observational cohort study. J Cyst Fibros 2005;4:35–40.
[30] Lipsuma JJ. Update on the Burkholderia cepacia complex. Curr Opin Pulm Med 2005;11:528–5.
[31] Com G, Carroll JL, Castro MM, Tang X, Jambhekar S, Berlinski A. Predictors and outcome of low initial forced expiratory volume in 1 second measurement in children with cystic fibrosis. J Pediatr 2014;164:832–8.
[32] Goss CH, Mayer-Hamblett N, Atiken ML, Rubenfeld GD, Ramsey BW. Association between Stenotrophomonas maltophilia and lung function in cystic fibrosis. Thorax 2004;59:955–9.
[33] Hansen CR. Stenotrophomonas maltophilia: to be or not to be a cystic fibrosis pathogen. Curr Opin Pulm Med 2012;18:628–31.
[34] Vaters V, Atenafu EG, Salazar JG, Lu A, Yao Y, Matukas L, et al. Chronic Stenotrophomonas maltophilia infection and exacerbation outcomes in cystic fibrosis. J Cyst Fibros 2012;11:8–13.
[35] De Baets F, Schelstraete P, Van Daele S, Haerynck F, Vaneechoutte M. Achromobacter xylosoxidans in cystic fibrosis: prevalence and clinical relevance. J Cyst Fibros 2007;6:75–8.
[36] Lambiase A, Catania MR, Del Pezzo M, Rossano F, Terlizzi V, Sepe A, et al. Achromobacter xylosoxidans: to be or not to be a cystic fibrosis pathogen. Curr Opin Pulm Med 2012;18:628–31.
[37] Molenberghs G. Applied longitudinal analysis. J Am Stat Assoc 2005;100:709–10.