

Predictors of Pulmonary Exacerbations in Patients with Cystic Fibrosis Infected with Multi-Resistant Bacteria.

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Abstract:

Background: This study examined characteristics of adult and adolescent cystic fibrosis patients to determine factors that would be associated with an increased risk of pulmonary exacerbations.

Methods: We recruited 249 cystic fibrosis patients who were infected with multi-drug resistant bacteria and prospectively followed them for up to 4.5 years until they experienced a pulmonary exacerbation severe enough to require intravenous antibiotics. Multivariable regression analyses were used to compare characteristics of patients who experienced an exacerbation with those who did not.

Results: Among the 249 patients, 124 (50%) developed a pulmonary exacerbation during the first year and 154 (62%) experienced an exacerbation during the 4 ½ year study period. Factors predictive of exacerbations in a multivariable survival model were younger age (OR 0.98, 95% CI 0.96-0.99), female gender (OR 1.45, 95% CI 1.07-1.95), lower FEV₁ (OR 0.98, 95% CI 0.97-0.99), and previous history of multiple pulmonary exacerbations (OR 3.16, 95% CI 1.93-5.17). Chronic use of inhaled corticosteroids was associated with an increased risk of exacerbation (OR 1.92, 95% CI 1.00-3.71) during the first study year.

Conclusions: Patients who experience pulmonary exacerbations are more likely to be younger, female, using inhaled steroids, have a lower FEV₁ and a history of multiple previous exacerbations. Knowledge of these risk factors will allow better identification and closer monitoring of patients who are at high risk of exacerbations.

Background

Patients with cystic fibrosis have viscous pulmonary secretions and decreased mucociliary clearance, resulting in chronic airway infection and bronchiectasis.[1] Although there have been steady, significant improvements in median survival over the past decades, premature mortality in CF patients is still common due to chronic respiratory infection and subsequent respiratory failure.[2]

Pulmonary disease in cystic fibrosis is characterized by chronic airway infection. Increasingly, patients are being infected with multi-resistant bacterial pathogens, including *Pseudomonas aeruginosa* and *Burkholderia cepacia*, that are resistant to all antibiotics in at least 2 of 3 major anti-pseudomonal antibiotic drug classes.[3]

Chronic bacterial airway infections in patients with CF generally follow a smoldering course punctuated by acute, unpredictable, pulmonary exacerbations that are characterized by worsening cough, increased sputum production and increased dyspnea.[3][4] Treatment of severe pulmonary exacerbations often requires hospital admission and intravenous antibiotic therapy, which negatively affects health-related quality of life[5] and contributes to significant health care costs.[6][7] Furthermore, pulmonary exacerbations are associated with impaired sleep and neurocognitive abilities[8] and with increased patient mortality.[9][10]

To date, no studies have systematically examined patient factors associated with pulmonary exacerbation. In a retrospective study, Schechter et al.[11] found that American CF patients with lower socioeconomic status were more likely to require treatment for pulmonary exacerbation. The Schechter study did not examine other characteristics, such as age, gender, lung function, previous CF complications, or medication use, all of which may affect the risk of pulmonary exacerbation.

This prospective study examined characteristics of adult CF patients infected with multi-drug resistant bacteria to determine patient factors that would predict increased risk for pulmonary exacerbation. Determination of risk factors associated with pulmonary exacerbations could allow for early identification and close monitoring of at-risk patients.

Methods

Patients

Patients were recruited as part of a clinical trial that evaluated combination antibiotic susceptibility testing for treatment of pulmonary exacerbations in cystic fibrosis (Aaron et al, Lancet 2005).[12] We recruited patients from ten Canadian and two Australian cystic fibrosis clinics with a confirmed diagnosis of cystic fibrosis who were known to be infected with multi-drug resistant bacteria. Patients were excluded from the study if they were unable to provide informed consent, were less than 12 years old, pregnant, on continuous home IV antibiotic therapy, or had previously undergone lung transplantation.

Procedures

Recruitment of study patients began in July 2000. At enrolment, research nurses at each study site completed a detailed, standardized, baseline questionnaire for each patient that included the following: 1) age, gender, height, weight, and body-mass index; 2) number of recent hospitalizations, presence of physician-diagnosed CF-associated diabetes mellitus, pancreatic insufficiency, or liver disease; and 3) use of chronic (> 2 months' use) inhaled or oral antibiotics, use of inhaled bronchodilators, inhaled

corticosteroids, insulin, DNase or prednisone. In addition lung function was measured in the pulmonary function lab and sputum bacterial cultures and sensitivities were done at enrolment.

After enrolment, patients were followed prospectively every 3 months for up to 4.5 years. At each clinic visit, patients provided a sputum sample for culture. Patients were followed until their first pulmonary exacerbation requiring intravenous antibiotics, or, for those patients who did not exacerbate, until the end of the study period (December 31, 2004). Patients who provided no further sputum samples or who were lost to follow-up were censored three months after their last documented study clinic visit.

A pulmonary exacerbation was defined as an acute exacerbation of pulmonary symptoms that in the opinion of the patient's CF physician was severe enough to require intravenous antibiotics. All exacerbations also had to fulfill criteria published by the 1994 Cystic Fibrosis Foundation Microbiology and Infectious Disease Consensus Conference [3] including the presence of at least three of the following 11 new findings or changes in clinical status when compared to the most recent baseline visit: increased cough; increased amount (or change in appearance of) sputum; decreased exercise tolerance; school or work absenteeism; fever ($\geq 38^{\circ}\text{C}$ for 4 h in a 24-h period); weight loss ($\geq 1\text{ kg}$ or 5% of body weight); increased respiratory rate or work of breathing; new wheeze or crackles; decrease in FEV₁ of $\geq 10\%$; decrease in O₂ saturation of $\geq 10\%$ (compared to baseline within the past 3 months); or new chest radiograph findings.

Informed written consent was obtained from all patients. The Research Ethics Boards of each hospital approved data collection for the purposes of the randomized clinical trial and further ethical approval was obtained for the analysis of this study from the Ottawa Hospital Research Ethics Board.

Statistical Analysis

Baseline characteristics of patients with and without pulmonary exacerbation were compared by univariate analysis. Quantitative variables were summarized as means \pm standard deviation while qualitative variables were given as frequency and percentages. Odds ratios and 95% confidence intervals were calculated for each variable separately, and a Bonferroni adjustment was made to account for multiple univariate comparisons so that P values of ≤ 0.0056 were taken to be significant.

Multivariable logistic regression models were generated to look at one-year risk factors for exacerbation. In addition, Cox proportional hazards models were generated to look at survival time to first exacerbation for the entire study duration. SAS version 9.1 (SAS Institute Inc. Cary, North Carolina) was used for all statistical procedures. For the multivariate models our approach was to include all potentially relevant clinical prognostic risk factors in the model. We selected variables that were 1) deemed clinically important and 2) that previous studies had suggested were risk factors for other poor clinical outcomes in CF patients. We did not formally assess model fit as our model was built on clinically, not statistically, meaningful criteria. Thus, multiple models were not developed or compared. Our goal was not to produce a clinical prediction rule but rather to elucidate the associations of postulated risk factors and pulmonary exacerbation.

Appropriate interaction terms such as age*FEV1 were tested in the models and retained if significant. Odds ratios and hazard ratios and their 95% confidence intervals were calculated for variables included in the logistic model and Cox proportional hazards model. P values of < 0.05 were taken to be significant.

Results

Two-hundred and fifty-one cystic fibrosis patients were recruited from eight Canadian and two Australian centers for the clinical trial but two patients were excluded from this study analysis: one because pulmonary exacerbation occurred one day after study enrolment, and the second because the recorded date of exacerbation was prior to the collection of baseline data (Figure 1).

Most of the 249 included patients were adults, only 7 patients (3%) were younger than age 18 at entry into the study. After 12 months of prospective observation 124 of 249 patients (50%) had experienced a pulmonary exacerbation requiring intravenous antibiotics. During the entire 4 ½ year study period, a total of 154 patients (62%) developed at least one pulmonary exacerbation (Figure 1). The median time to exacerbation in this group was 144 days (range 56-1577 days). The remaining 95 patients were observed for a median duration of 815 days, and these patients did not experience a pulmonary exacerbation requiring intravenous antibiotics during the study period.

Table 1 compares baseline data among the 249 patients. Patients with pulmonary exacerbations were more likely to be younger (mean age 30.1 vs 33.5 years, $p=0.002$), female (OR 3.37, 95% CI 1.92-5.90), pancreatic insufficient (OR 4.31, 95% CI 1.47-12.65), and have a lower body mass index (21.2 vs. 22.9, $p=0.002$) than those who did not exacerbate during the study period. In addition, patients who experienced an exacerbation had a lower baseline FEV₁ (48% predicted vs. 63% predicted, $p<0.0001$) and a lower baseline FVC (66% predicted vs. 77% predicted, $p=0.0002$) and they had experienced more courses of intravenous antibiotics for pulmonary exacerbations in the 24-month period prior to study enrolment. Patients who experienced pulmonary exacerbations were also more likely to be taking inhaled corticosteroid (OR 3.12, 95% CI 1.81-5.35). Use of DNase (OR 1.85, 95% CI 1.03-3.33) or inhaled tobramycin (OR 1.82, 95% CI 1.05-3.13) was also somewhat more likely in the group who exacerbated, however these variables did not meet our predetermined level of significance of $P < 0.0056$ for univariate comparisons.

The prevalence of physician-diagnosed CF-related diabetes mellitus or physician-diagnosed CF-related liver disease did not significantly differ between the two groups. Acquisition of a new bacterial species during the study period was rare (occurring in only 5% and 7% of patients in the exacerbating and non-exacerbating groups) and was not associated with increased risk of exacerbation ($P = 0.49$).

A multivariable Cox proportional hazards model was used to examine survival time to first exacerbation for the entire study duration (Table 2). Factors predictive of exacerbations in the multivariable survival model were younger age (OR 0.98, 95% CI 0.96-0.99), female gender (OR 1.45, 95% CI 1.07-1.95), lower FEV₁ (OR 0.98, 95% CI 0.97-0.99), and previous history of multiple pulmonary exacerbations (OR 3.16, 95% CI 1.93-5.17). Patients infected with *S. maltophilia* and *A. xylosidans* bacteria (ie. bacteria other than *B. cepacia* or *P. aeruginosa*) also were more likely to have accelerated times to first exacerbation. Significant interactions between age and lung function were not found.

Patients who experienced a pulmonary exacerbation within one year of entry into the study were compared with those who remained exacerbation-free over the first year in a logistic regression model that mutually controlled for other patient factors (Table 3). Within one year of entering the study, 124 patients (50%) experienced a pulmonary

exacerbation. Significant risk factors that predicted an increased risk of exacerbation within the first year were younger age (OR 0.93, 95% CI 0.89-0.97), lower FEV₁ (OR 0.97, 95% CI 0.94-1.00), use of inhaled corticosteroids (OR 1.92, 95% CI 1.00-3.71) and history of at least two pulmonary exacerbations requiring intravenous antibiotics within the previous 24 months (OR 7.74, 95% CI 2.94-20.39). Patients using chronic oral azithromycin were less likely to develop a pulmonary exacerbation during the first year (OR 0.28, 95% CI 0.11-0.72). Infecting organism was not a significant risk factor for exacerbation over one year.

Discussion

This is the first published study to comprehensively examine patient-related risk factors for cystic fibrosis pulmonary exacerbations. One previous retrospective study found that patients with lower socioeconomic status were more likely to require treatment for pulmonary exacerbation [11]; however, the authors did not examine other patient characteristics, such as age, gender, lung function, previous CF complications, or medication use, all of which may affect the rate of pulmonary exacerbation.

Our study suggests that female CF patients are at greater risk of pulmonary exacerbation than their male counterparts. Although no other published studies have looked at gender as a predictor of pulmonary exacerbation, many studies in cystic fibrosis patients have identified female gender as a significant risk factor for mortality. [9] [13][14][15] The fact that female CF patients may be more predisposed to exacerbations may help explain why they also have shorter median life expectancies, since exacerbations are known to be associated with premature mortality.

The impact of patient age on the risk of death or pulmonary exacerbation has been a matter of debate in the cystic fibrosis literature. Kerem et al. studied 673 Canadian children and found an increased risk of death in younger patients after controlling for other patient factors. [14] A clinical trial of rhDNAse for cystic fibrosis found that patients 17 to 23 years of age had a higher incidence of pulmonary exacerbations regardless of treatment-group assignment. [18] The data from our study similarly suggest that younger age is associated with an increased risk of pulmonary exacerbation after controlling for other factors. Patients that are more severely affected by cystic fibrosis may have earlier, more frequent pulmonary exacerbations and earlier death, resulting in a survivor effect in which patients with phenotypically milder forms of CF may live longer and be at less risk for severe exacerbations.

Impaired lung function has been repeatedly shown to be the best predictor of death in cystic fibrosis patients.[9] [13][14] Our data suggests that CF patients with lower baseline FEV₁ (% predicted) are also more likely to experience severe pulmonary exacerbations. This is not unexpected since patients with lower baseline lung function would be less likely to tolerate acute viral or bacterial infections that can precipitate pulmonary exacerbations.

Our prospective study also demonstrated that a history of recent pulmonary exacerbation was associated with future pulmonary exacerbation. This finding, although perhaps intuitive, has not been documented in the literature. A logistic regression model by Liou et al [9] showed that a higher annual number of pulmonary exacerbations predicted worse survival. However, a similar study by Ellaffi et al[16] showed that pulmonary exacerbation did not affect disease progression in patients who survived to one year after severe pulmonary exacerbation. Results of our study clearly suggest that a

previous history of exacerbations was highly predictive of future exacerbations. Clinical investigators need to be aware of this finding when they design clinical trials with exacerbation as an endpoint.

Clinical trials have previously shown that CF patients treated with inhaled tobramycin[17], and DNase[18] , were less likely to require intravenous antibiotics for pulmonary exacerbation. In our study, patients taking inhaled tobramycin or DNase had a slightly higher risk of pulmonary exacerbation in the univariate analysis, but this effect was not significant when other patient factors were controlled for in multivariate models. The apparent association from the univariate analysis may reflect confounding by indication. That is, use of these inhaled medications may be a marker for patients with more severe baseline disease who are on near-maximal therapy and who may be more likely to experience pulmonary exacerbation independent of medication use. Some degree of confounding by indication is likely because use of DNase and tobramycin was not associated with an increased odds ratio of exacerbation in multivariate models which controlled for other risk factors associated with disease severity, such as lung function and gender.

In contrast, the evidence for use of inhaled corticosteroids in the management of cystic fibrosis is unclear.[19] Although inflammation plays a major role in the pathophysiology of cystic fibrosis lung disease, studies have not been done to suggest that inhaled steroids exert any clinically relevant anti-inflammatory effects in CF patients. In fact, a recent study suggests that withdrawal of inhaled corticosteroids in CF patients does no harm, raising further questions about the role of this medication.[20] In our one-year logistic model, inhaled corticosteroid use was associated with a higher risk of pulmonary exacerbation, even when additional factors such as age, gender, and lung function were controlled for. While interesting, this association will require further study to determine if there is a potential causal relationship. Again, it is still possible that this association may simply reflect confounding by indication.

The effect of chronic oral azithromycin in cystic fibrosis patients infected with *Pseudomonas aeruginosa* was described by Saiman et al.[21] who found that patients taking this medication were at a lower risk of pulmonary exacerbation. Wolter et al.[22] also observed fewer pulmonary exacerbations in CF patients taking regular oral azithromycin in a study group in which 83% of patients were infected with *P. aeruginosa*. Our study of patients infected with multi-drug resistant bacteria including, but not limited to, *Pseudomonas aeruginosa*, also demonstrated an association between chronic azithromycin use and lower risk of pulmonary exacerbation at one year, after controlling for other patient factors in a logistic regression model. This effect is particularly striking given that the use of other commonly prescribed medications (tobramycin, DNase, corticosteroids) was associated with at best, no effect, and at worst, and increased risk of pulmonary exacerbation in the CF patients studied. The results of this study suggest that further research on azithromycin use in cystic fibrosis patients infected with organisms other than *Pseudomonas aeruginosa* is indicated.

A potential limitation of our study is that we only enrolled cystic fibrosis patients infected with multi-drug resistant bacteria. Patients with multi-resistant organisms may be very different from those infected with pan-sensitive *P. aeruginosa* and those not infected with *P. aeruginosa*. A recent study by Lechtzin et al. has suggested that 25-45% of adults with cystic fibrosis have multi-resistant infections and that these patients have accelerated rates of lung function decline when compared to patients with non-resistant

strains.[23] Cystic fibrosis patients with multi-resistant infections provide a good model for patients with severe disease, but this study would need to be repeated in patients with milder disease to see if the same associations hold true.

A second potential limitation of our study is that we enrolled mostly adult CF patients, along with a small number of adolescent patients. Our study is not generalizable to children with CF and would need to be repeated in a pediatric population to see if the same associations hold true.

Pulmonary exacerbations are associated with poor quality of life, declines in cognitive status, increased health-care costs and increased patient mortality.[8][9] Clearly, studies of factors that either predispose or protect cystic fibrosis patients from pulmonary exacerbation have the potential to significantly affect both patient outcomes and health-care system outcomes. The results of our prospective study suggest that age, gender, lung function, history of previous exacerbations, and use of inhaled corticosteroids are important factors that are associated with pulmonary exacerbations in cystic fibrosis patients. Knowledge of these risk factors would allow for early identification and closer monitoring of patients with high-risk profiles. Hopefully close monitoring of high-risk patients and early identification of worsening pulmonary symptoms would allow timely therapeutic interventions with oral antibiotics and/or physiotherapy to prevent severe exacerbations.

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Figure Legend:

Figure 1: Participant Flow Sheet.

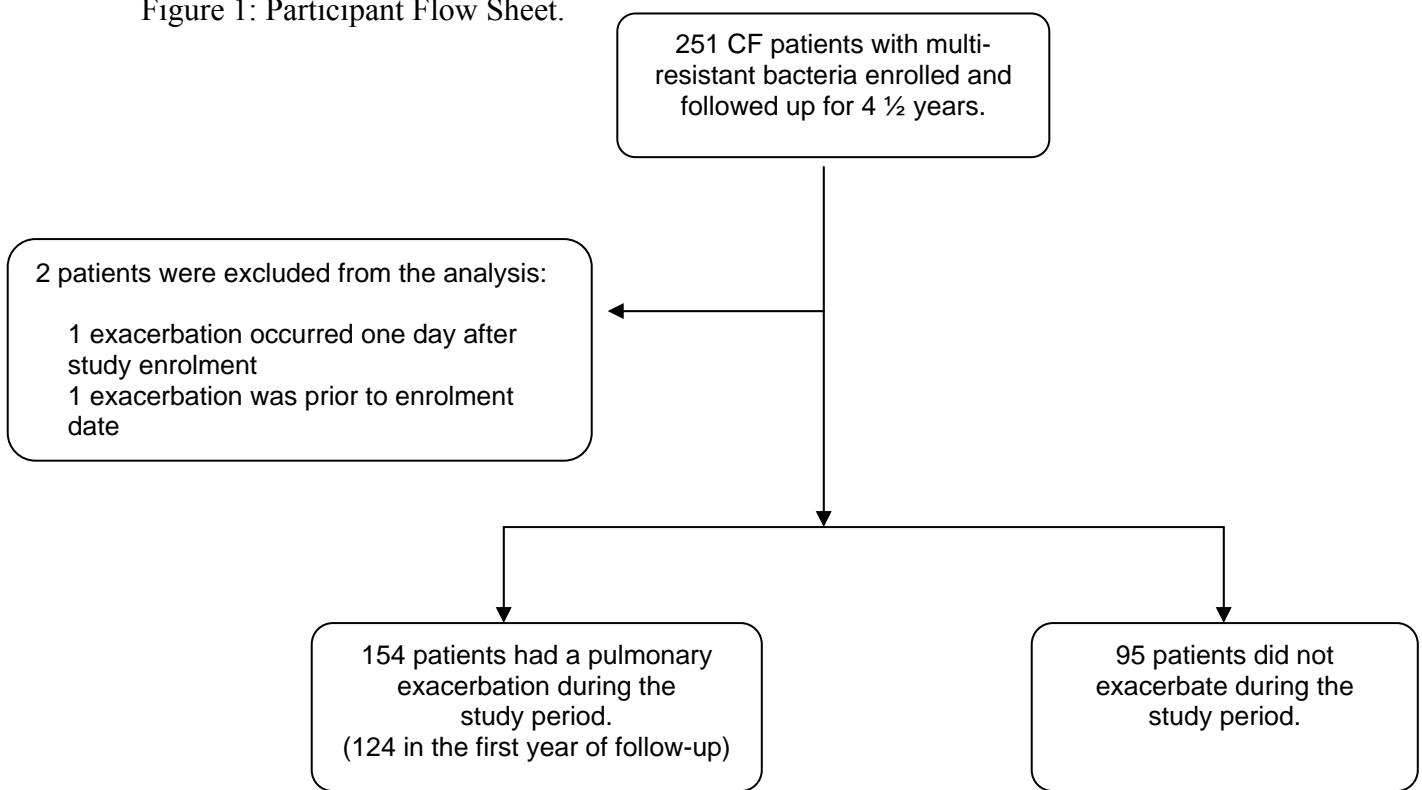


Table 1. Patient Characteristics

Patient Characteristic	Exacerbated (n=154)	Did not exacerbate (n=95)	Odds Ratio (95% CI)	P-Value
Mean Age (SD)	30.1 (13.8)	33.5 (8.8)	0.95 (0.92, 0.98)	0.002
Female Gender (%)	82 (53%)	24 (25%)	3.37 (1.92, 5.90)	<0.0001
Body Mass Index (kg/m ²) (SD)	21.2 (4.3)	22.9 (3.1)	0.88 (0.82, 0.96)	0.002
Lung function				
FEV ₁ % predicted [‡] (SD)	48.3 (18.1)	63.0 (20.2)	0.96 (0.95, 0.98)	<0.0001
FVC % predicted (SD)	66.4 (20.3)	76.9 (19.2)	0.97 (0.96, 0.99)	0.0002
CF-related diabetes mellitus	35 (22.7%)	18 (18.9%)	1.26 (0.67, 2.38)	0.48
CF-related pancreatic insufficiency	149 (96.8%)	83 (87.4%)	4.31 (1.47, 12.65)	0.008
CF-related liver disease	18 (11.6%)	8 (8.4%)	1.44 (0.60, 3.45)	0.41
Courses of IV antibiotics for pulmonary exacerbation in past 24 months				
0	38 (24.7%)	61 (64.2%)	-	-
1	30 (19.5%)	19 (20.0%)	2.54 (1.26, 5.12)	0.001
2-3	40 (26.0%)	8 (8.4%)	8.03 (3.40, 18.98)	<0.0001
≥3	46 (29.9%)	7 (7.4%)	10.55 (4.32, 25.75)	<0.0001
Bacteria in sputum at enrolment				
Burkholderia cepacia complex (BC)	55 (35.7%)	38 (40%)	-	-
Pseudomonas aeruginosa (PA)	78 (50.6%)	38 (40%)	1.42 (0.81, 2.50)	0.26
Both BC & PA	6 (3.9%)	8 (8.4%)	0.52 (0.17, 1.62)	0.26
Other	15 (9.7%)	11 (11.6%)	0.94 (0.39, 2.27)	0.89
New bacterial species in sputum during study	8 (5.2%)	7 (7.4%)	0.69 (0.24, 1.97)	0.49
Burkholderia cepacia complex	2	0		
Pseudomonas aeruginosa	3	6		
Stenotrophomonous maltophilia	1	0		
Achromobacter xylosoxidans	2	1		
None	146 (94.8%)	88 (92.6%)		
Medications used chronically:				
Inhaled corticosteroid	89 (57.8%)	29 (30.5%)	3.12 (1.81, 5.35)	<0.0001
DNase	53 (34.4%)	21 (22.1%)	1.85 (1.03, 3.33)	0.04
Inhaled antibiotics				
None	54 (35.1%)	49 (51.6%)	-	-
Tobramycin	78 (50.6%)	39 (41.1%)	1.82 (1.05, 3.13)	0.03
Colymycin	8 (5.2%)	2 (2.1%)	3.63 (0.74, 17.9)	0.11
Tobramycin & Colymycin	14 (9.1%)	5 (5.3%)	2.54 (0.85, 7.57)	0.09
Oral antibiotics				
None	101 (65.6%)	66 (69.5%)	-	-
Azithromycin	21 (13.6%)	15 (15.8%)	0.92 (0.44, 1.90)	0.81
Other	19 (12.3%)	11 (11.6%)	1.13 (0.51, 2.52)	0.77
Azithromycin & Other	13 (8.4%)	3 (3.2%)	2.83 (0.78, 10.32)	0.11

[‡] FEV₁= forced expiratory volume in one second; FVC = forced vital capacity

Table 2. Cox Proportional Hazards Model of Time to First Exacerbation.

Patient Characteristic	Hazard Ratio (95% CI)	P-Value
Age [†]	0.98 (0.96, 0.998)	0.03
Female Gender	1.45 (1.07, 1.95)	0.02
Body Mass Index (kg/m ²)	0.99 (0.95, 1.05)	0.94
Lung function		
FEV ₁ (% predicted) [‡]	0.98 (0.97, 0.995)	0.006
FVC (% predicted)	1.01 (0.995, 1.02)	0.23
CF-related diabetes mellitus	0.79 (0.56, 1.11)	0.17
Courses of IV antibiotics for pulmonary exacerbation in past 24 months		
0	-	-
1	1.51 (1.03, 2.21)	0.03
2-3	1.64 (1.07, 2.52)	0.02
>3	3.16 (1.93, 5.17)	<0.0001
	P value for trend < 0.0001	
Bacteria in sputum at enrolment		
Burkholderia cepacia complex (BC)	0.39 (0.24, 0.64)	0.0002
Pseudomonas aeruginosa (PA)	0.68 (0.43, 1.08)	0.1
Both BC & PA	0.29 (0.14, 0.59)	0.0008
Other	-	-
New bacterial species acquired in sputum during study	1.03 (0.82, 1.28)	0.82
Medications used chronically:		
Inhaled corticosteroid	1.13 (0.86, 1.48)	0.39
DNAse	1.28 (0.92, 1.78)	0.14
Inhaled antibiotics	0.92 (0.69, 1.21)	0.54
Oral antibiotics		
None	-	-
Azithromycin	1.04 (0.70, 1.55)	0.83
Other	0.89 (0.58, 1.37)	0.61

[†] FEV₁= forced expiratory volume in one second; FVC = forced vital capacity

Table 3. Multivariable Logistic Model of Factors Predicting Pulmonary Exacerbation During the First Year of Follow-up.

Patient Characteristic	Odds Ratio (95% CI)	P-Value
Age [†]	0.93 (0.89, 0.97)	0.002
Female Gender	1.37 (0.69, 2.72)	0.37
Body Mass Index (kg/m ²)	0.92 (0.83, 1.01)	0.07
Lung function		
FEV ₁ (% predicted) [‡]	0.97 (0.94, 1.00)	0.05
FVC (% predicted)	1.02 (0.99, 1.05)	0.14
CF-related diabetes mellitus	0.81 (0.36, 1.81)	0.61
Courses of IV antibiotics for pulmonary exacerbation in past 24 months		
0	-	-
1	2.30 (0.99, 5.31)	0.05
2-3	7.74 (2.94, 20.39)	<0.0001
>3	20.81 (6.37, 67..92)	<0.0001
		P value for trend < 0.0001
Bacteria in sputum at enrolment		
Burkholderia cepacia complex (BC)	0.96 (0.30, 3.09)	0.94
Pseudomonas aeruginosa (PA)	0.79 (0.25, 2.47)	0.68
Both BC & PA	0.63 (0.10, 4.00)	0.63
Other	-	-
New bacterial species acquired in sputum during study	0.50 (0.13, 1.93)	0.32
Medications used chronically:		
Inhaled corticosteroid	1.92 (1.00, 3.71)	0.05
DNase	1.24 (0.56, 2.76)	0.59
Inhaled antibiotics	1.46 (0.74, 2.89)	0.28
Oral antibiotics		
None	-	-
Azithromycin	0.28 (0.11, 0.72)	0.01
Other	0.87 (0.31, 2.46)	0.79

[†] FEV₁= forced expiratory volume in one second; FVC = forced vital capacity