

Failure to Recover to Baseline Pulmonary Function after Cystic Fibrosis Pulmonary Exacerbation

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Rationale: Patients with cystic fibrosis periodically experience pulmonary exacerbations. Previous studies have noted that some patients' lung function (FEV₁) does not improve with treatment.

Objectives: To determine the proportion of patients treated for a pulmonary exacerbation that does not recover to spirometric baseline, and to identify factors associated with the failure to recover to spirometric baseline.

Methods: Cohort study using the Cystic Fibrosis Foundation Patient Registry from 2003–2006. We randomly selected one pulmonary exacerbation treated with intravenous antibiotics per patient and compared the best FEV₁ in the 3 months after treatment with the best FEV₁ in the 6 months before treatment. Recovery to baseline was defined as any FEV₁ in the 3 months after treatment that was greater than or equal to 90% of the baseline FEV₁. Multivariable logistic regression was used to estimate associations with the failure to recover to baseline FEV₁.

Measurements and Main Results: Of 8,479 pulmonary exacerbations, 25% failed to recover to baseline FEV₁. A higher risk of failing to recover to baseline was associated with female sex; pancreatic insufficiency; being undernourished; Medicaid insurance; persistent infection with *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, or methicillin-resistant *Staphylococcus aureus*; allergic bronchopulmonary aspergillosis; a longer time since baseline spirometric assessment; and a larger drop in FEV₁ from baseline to treatment initiation. **Conclusions:** For a randomly selected pulmonary exacerbation, 25% of patients' pulmonary function did not recover to baseline after treatment with intravenous antibiotics. We identified factors associated with the failure to recover to baseline, allowing clinicians to identify patients who may benefit from closer monitoring and more aggressive treatment.

Keywords: cystic fibrosis; pulmonary exacerbation; pulmonary function tests; spirometry; antibiotics

Lung disease is the major source of morbidity and mortality for patients with cystic fibrosis (CF) (1). One of the hallmarks of CF lung disease is the pulmonary exacerbation, characterized by an increase in pulmonary symptoms, decrease in pulmonary function, loss of energy, weight loss, and changes in physical findings (2). Pulmonary exacerbations have been linked to increased mortality (3, 4); higher health care costs (5); reduced quality of life (6); and a faster subsequent decline in pulmonary function (FEV₁) (7). In

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung function improves during treatment of pulmonary exacerbations in patients with cystic fibrosis. However, it is not clear how often lung function returns to previous baseline levels after treatment of a pulmonary exacerbation.

What This Study Adds to the Field

For a randomly selected pulmonary exacerbation, 25% of patients' pulmonary function did not recover to baseline within the 3 months after treatment with intravenous antibiotics. We identified several patient characteristics that are associated with a higher risk of failing to recover to baseline.

2008, 38% of patients with CF in the Cystic Fibrosis Foundation Patient Registry (CFFPR) were treated with intravenous (IV) antibiotics for at least one pulmonary exacerbation (8).

Previous studies have noted that some patients' FEV₁ values do not improve with IV antibiotic treatment (9–11). In a retrospective analysis of the placebo arm of an inhaled tobramycin trial, Smith and coworkers (9) showed that 23 out of 77 patients' FEV₁ did not improve after treatment with IV antibiotics to levels achieved at the clinic visit before the exacerbation. In a retrospective single-center study, we recently showed that one in four patients with CF treated with IV antibiotics for a pulmonary exacerbation did not recover to FEV₁ levels achieved in the 6 months before treatment (11). Identifying patients who are at risk of not recovering to previously established pulmonary function levels would provide an opportunity to prevent this from occurring. Thus, the purposes of this study were to determine the proportion of patients in a nationwide cohort that does not recover to previous baseline pulmonary function levels and to determine if factors known to be associated with decreased pulmonary function among patients with CF were also associated with the failure to recover to previous pulmonary function levels after a pulmonary exacerbation. The CFFPR includes individuals with CF followed in all U.S. CF Foundation-accredited centers (8). We used the CFFPR to determine the proportion of patients that recovered to pulmonary function levels achieved before the exacerbation. We developed multivariable logistic regression models to identify associations between patient and treatment characteristics and the failure to recover to previous baseline pulmonary function levels. The results of this study were previously reported in abstract form (12).

METHODS

Population

We included individuals in the CFFPR from January 1, 2003, through December 31, 2006, who were at least 6 years old, treated for at least

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one pulmonary exacerbation with IV antibiotics, and had at least 12 months of data in the CFFPR before any pulmonary exacerbations during the study. Subjects were excluded if they had a solid-organ transplantation or died before the end study date. Data are entered into the CFFPR at each clinical encounter. We analyzed one randomly selected pulmonary exacerbation per subject. Consecutive pulmonary exacerbations with less than or equal to 3 weeks between IV antibiotics were treated as a single event.

Design and Procedures

Percent predicted values of FEV₁ were calculated using Hankinson and Wang equations (13, 14). Baseline FEV₁ was defined as the best FEV₁ in the 6 months before the pulmonary exacerbation. Recovery to baseline was defined as any FEV₁ in the 3 months after treatment that was greater than or equal to 90% of the baseline FEV₁. This definition was chosen *a priori* to account for week-to-week FEV₁ variability (15).

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. We developed a multivariable logistic regression model to identify associations with the failure to recover to baseline after a review of the literature to find factors associated with lower pulmonary function or failure to recover to baseline pulmonary function (7, 9, 11, 16–23). Age group, sex, baseline FEV₁, time since baseline FEV₁, and Medicaid insurance were included *a priori* in a base model to account for possible confounding. We retained the following potential confounders in the final model if a likelihood ratio test *P* value < 0.05 was obtained when added individually to the base model: allergic bronchopulmonary aspergillosis (ABPA); body mass index; persistent infection with *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, methicillin-resistant *Staphylococcus aureus* (MRSA), or nontuberculous *Mycobac-*

teria; pancreatic insufficiency; diabetes mellitus; ΔF508 status; CF center size; and interactions between age and *P. aeruginosa*, sex, and baseline FEV₁. A persistent infection was defined as at least two positive cultures in the 12 months before the pulmonary exacerbation. Being undernourished was defined as a body mass index less than 18.5 kg/m² for adults or less than the 5th percentile of the Centers for Disease Control and Prevention growth charts for children (24). Medicaid insurance was used as a surrogate for low socioeconomic status (17). See the online supplement for additional covariate definitions.

Sensitivity analyses were performed to assess the impact of including (1) one positive culture in the previous 12 months for *P. aeruginosa*, *B. cepacia* complex, and MRSA; (2) the number of pulmonary exacerbations in the prior 6 months; (3) the duration of pulmonary exacerbations in the prior 6 months; and (4) treatment duration of the analyzed pulmonary exacerbation. A secondary analysis was performed on the subset of patients who had FEV₁ measured at treatment initiation to assess if the decline in FEV₁ before treatment was associated with the outcome.

A *P* value < 0.05 was considered statistically significant for all analyses. An odds ratio greater than 1 indicates an increased risk of failing to recover to baseline FEV₁. Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC). The Institutional Review Board at Seattle Children's Hospital approved the study.

RESULTS

Cohort Characteristics

There were 27,027 individuals with CF in the CFFPR between 2003 and 2006. Of the 8,479 evaluable subjects with pulmonary exacerbations, a total of 2,159 (25%) failed to recover to baseline FEV₁ within the 3 months after treatment (Figure 1).

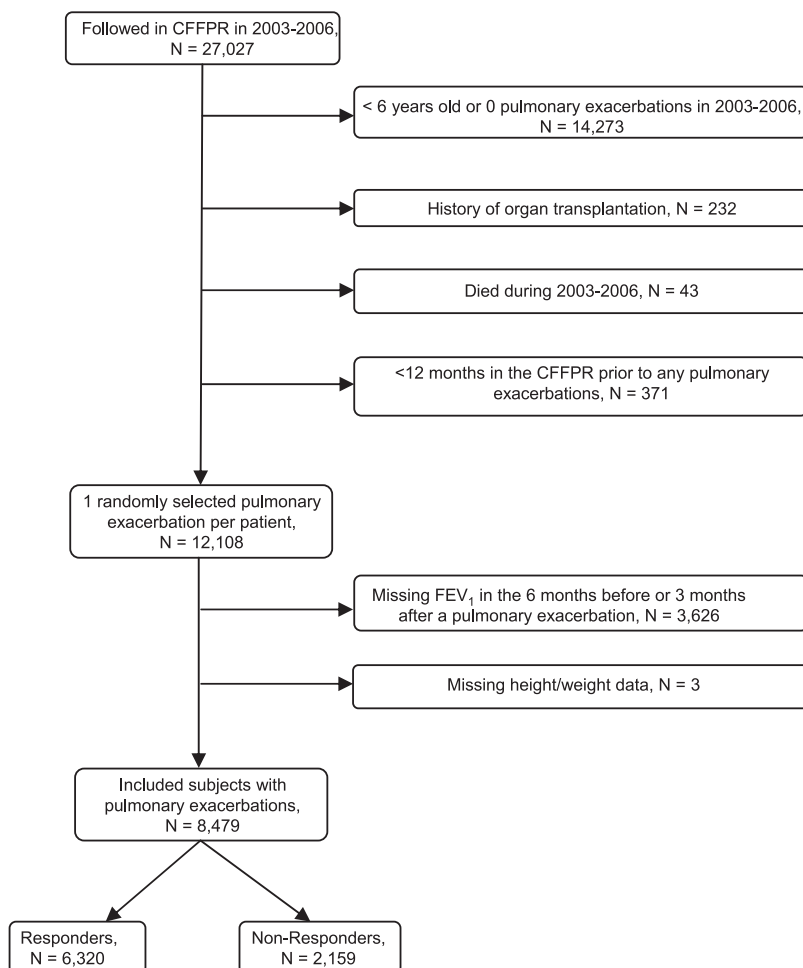


Figure 1. Diagram of study cohort.

Of those who failed to recover to baseline within the 3 months after treatment, a total of 1,629 (75%) still had not recovered to baseline in the 6 months after treatment, and there were 1,250 (58%) whose pulmonary function did not recover to baseline in the 12 months after treatment. Additionally, those who failed to recover within the 3 months after treatment had more frequent pulmonary exacerbations in the 3, 6, and 12 months after treatment ($P < 0.001$) (see Table E1 in the online supplement). Generally, patient characteristics were similar between those who recovered within the 3 months after treatment (responders) and those who did not (nonresponders), although there were many statistically significant differences given the large cohort size (Table 1). Nonresponders had a higher proportion of individuals who were female; undernourished; insured by Medicaid; had baseline FEV₁ less than 40% predicted; and were persistently infected with MRSA, *P. aeruginosa*, or multidrug-resistant *P. aeruginosa* (Table 1). Nonresponders began treatment after more time had passed from their baseline spirometric assessment (mean [SD] of 14.9 [7.3] weeks compared with 11.7 [8.1] weeks for responders; $P < 0.001$). At baseline, mean (SD) FEV₁ % predicted was minimally lower for nonresponders compared with responders (65.2 [27.1] compared with 67.4 [25.7], respectively; $P < 0.001$), but nonresponders had a substantially lower mean (SD) FEV₁ % predicted in the 3 months after treatment (51.9 [23.3] compared with 70.9 [25.6] for responders; $P < 0.001$).

Of the 8,479 total subjects, there were 4,391 subjects with FEV₁ measurements at the initiation of treatment. For nonresponders, the mean (SD) FEV₁ % predicted at treatment initiation was lower (52.1 [24.1] % predicted) than for responders (60 [23.4] % predicted; $P < 0.001$) (Figure 2). In addition, nonresponders had a larger mean (SD) relative drop in FEV₁ % predicted between baseline spirometric assessment

and treatment initiation (24% [17%] compared with 13% [15%] for responders; $P < 0.001$).

Final Model

The final multivariable logistic regression model for associations with the failure to recover to baseline pulmonary function is shown in Figure 3. Of the potential confounders tested, pancreatic insufficiency, ABPA, persistent infection with *P. aeruginosa*, *B. cepacia* complex, and MRSA, and CF center size were included in the final model. Being insured by Medicaid, undernourished, female, pancreatic insufficient, persistently infected with *P. aeruginosa*, *B. cepacia* complex, and MRSA, and ABPA were associated with an increased risk of failing to recover to baseline. Having baseline FEV₁ between 60 and 79% predicted and being cared for at large CF centers (>150 patients) were associated with a decreased risk of failing to recover to baseline.

Sensitivity Analysis

The results of the sensitivity analyses were consistent with the final model and are available in the online supplement (see Tables E2–E5). Having been treated for pulmonary exacerbations in the 6 months before the analyzed pulmonary exacerbation was also associated with the failure to recover to baseline. In addition, patients treated for at least 21 days during the analyzed pulmonary exacerbation had a higher odds ratio of failing to recover to baseline (odds ratio 1.58; 95% confidence interval, 1.30–1.92).

In a secondary analysis of the 4,391 subjects with FEV₁ measured at the initiation of treatment, we added the decline in FEV₁ between baseline spirometric assessment and treatment initiation to the final model. The odds ratio was 1.53 (95%

TABLE 1. COHORT CHARACTERISTICS BY RESPONDER AND NONRESPONDER STATUS

Characteristic	Category	Nonresponder (n = 2,159) N (%)	Responder (n = 6,320) N (%)	P Value
Female sex		1,153 (53.4)	3,209 (50.8)	0.03
Age group, yr	7–8	171 (7.9)	504 (8)	0.06
	9–12	323 (15)	1,101 (17.4)	
	13–17	525 (24.3)	1,401 (22.2)	
	18–24	566 (26.2)	1,627 (25.7)	
	25+	574 (26.6)	1,687 (26.7)	
White		2,069 (95.8)	6,053 (95.8)	0.9
Pancreatic insufficiency		2,076 (96.2)	5,970 (94.5)	0.002
ΔF508 mutation	Heterozygous	501 (23.2)	1,447 (22.9)	0.6
	Homozygous	977 (45.3)	2,957 (46.8)	
	Unknown/not present	681 (31.5)	1,916 (30.3)	
Medicaid insurance		1,054 (48.8)	2,636 (41.7)	<0.001
Persistent <i>P. aeruginosa</i> infection		916 (42.4)	2,295 (36.3)	<0.001
Multidrug-resistant <i>P. aeruginosa</i>		387 (17.9)	882 (14)	<0.001
Persistent <i>B. cepacia</i> complex infection		75 (3.5)	110 (1.7)	<0.001
Persistent methicillin-resistant <i>Staphylococcus aureus</i> infection		377 (17.5)	880 (13.9)	<0.001
Nontuberculous <i>Mycobacteria</i>		70 (3.2)	168 (2.7)	0.2
Allergic bronchopulmonary aspergillosis		153 (7.1)	342 (5.4)	0.004
Undernourished body mass index*		513 (23.8)	1,048 (16.6)	<0.001
Baseline FEV ₁	<40% predicted	482 (22.3)	1,124 (17.8)	<0.001
	40–59% predicted	740 (34.3)	2,183 (34.5)	
	60–79% predicted	472 (21.9)	1,639 (25.9)	
	≥80% predicted	465 (21.5)	1,374 (21.8)	
Cystic fibrosis–related diabetes mellitus		140 (6.5)	344 (5.4)	0.07
Cystic fibrosis center size	<50 patients	224 (10.4)	563 (8.9)	0.04
	51–150	1,124 (52.1)	3,235 (51.2)	
	150+	811 (37.5)	2,522 (39.9)	

* Being undernourished was defined as a body mass index less than 18.5 kg/m² for adults or less than 5th percentile of the Centers for Disease Control and Prevention growth charts for children.

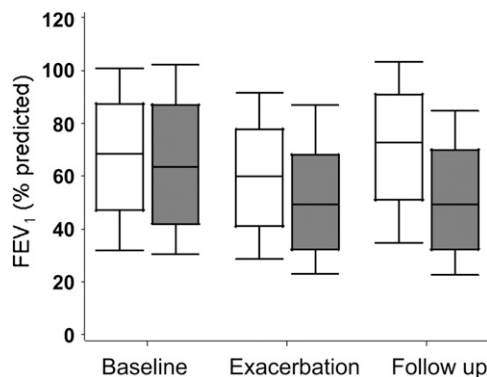


Figure 2. FEV₁ for nonresponders and responders at baseline, treatment initiation, and the best FEV₁ in the 3 months after treatment (n = 4,391). Responders are in white, nonresponders are in gray. The boxes represent the middle 50% of patients; the whiskers include all patients in each group. The horizontal line within the box represents the median FEV₁. The x axis represents three time points: the best FEV₁ in the 6 months before admission (baseline); FEV₁ at treatment initiation (exacerbation); and the best FEV₁ in the 3 months after treatment (follow-up).

confidence interval, 1.46–1.61) for every 10% relative decline in FEV₁ (e.g., 100% predicted at baseline to 90% predicted at treatment initiation or 50% predicted at baseline to 45% predicted at treatment initiation). In other words, adjusted for other covariates, the subjects whose FEV₁ had declined the most had the highest odds ratio for failing to recover to baseline pulmonary function. None of the other terms in the model were affected.

DISCUSSION

Our results show that, for a randomly selected pulmonary exacerbation from patients treated with IV antibiotics at US CF centers, one in four patients' pulmonary function did not recover within the 3 months after treatment to their baseline pulmonary function established in the 6 months before treatment. Several smaller studies have noted similar findings. In the review by Smith and coworkers (9) of the placebo arm of an inhaled tobramycin trial, 23 (30%) of 77 patients treated for a pulmonary exacerbation with intravenous antibiotics did not recover to the pulmonary function obtained at the clinic visit before treatment. Failure to recover was associated with longer time between the prior clinic visit and the initiation of treatment, and lower baseline pulmonary function. We recently showed that the failure to recover to baseline pulmonary function occurred in 24 (23%) of 104 patients treated at a single pediatric CF center (11). We also found an association with the failure to recover to baseline pulmonary function and Medicaid insurance status and a larger fall in FEV₁ before treatment initiation. This present study demonstrates that the failure to recover to baseline occurs frequently in CF centers across the United States.

The failure to recover to baseline pulmonary function may have significant short-term and long-term repercussions. Multiple studies have shown that any gains in pulmonary function after treatment of a pulmonary exacerbation may be lost over a period of days to weeks (25–28). Patients treated more frequently for pulmonary exacerbations experience a faster rate of FEV₁ decline (7). Patients with lower FEV₁ have more frequent pulmonary exacerbations (29). Patients who do not recover to baseline may therefore be at risk of never regaining

this lung function: in our study, 58% of subjects whose pulmonary function did not recover to baseline within 3 months after treatment still had not recovered to baseline when we extended the window of observation to include up to 12 months after treatment. It is unclear to what degree acute exacerbations of underlying lung disease and chronic decline between events individually contribute to pulmonary morbidity in CF. Our results combined with others' work support the contention that the acute pulmonary exacerbation is a critical event in determining the course of CF lung disease; further work is needed to confirm this hypothesis.

For our multivariable analysis, we chose factors available in the CFFPR that have been previously reported in the literature to be associated either with the failure to recover to baseline pulmonary function after a pulmonary exacerbation (age, time between baseline spirometric assessment and treatment, and Medicaid insurance) (9, 11), or with lower pulmonary function in patients with CF (Δ F508 status; female sex; pancreatic insufficiency; poor nutrition; diabetes mellitus; Medicaid insurance status; persistent infection with *P. aeruginosa*, *B. cepacia* complex, nontuberculous *Mycobacteria*, or MRSA; and ABPA) (7, 16–23). In the present study, the failure to recover to baseline pulmonary function was associated with several factors known to be associated with lower pulmonary function in patients with CF, namely female sex; pancreatic insufficiency; poor nutrition; Medicaid insurance status (a surrogate for low socioeconomic status); persistent infection with *P. aeruginosa*, *B. cepacia* complex, or MRSA; and ABPA. Our results indicate that the association between these clinical markers and a higher odds ratio of failing to recover to baseline pulmonary function may at least partially explain the reported associations between these clinical markers and poorer pulmonary function.

After adjusting for these covariates, the failure to recover to baseline was associated with a longer time between treatment initiation and baseline spirometric assessment, and a larger fall in FEV₁ between the baseline assessment and treatment initiation. These findings reveal opportunities to intervene therapeutically and promote recovery to baseline pulmonary function. Earlier identification of pulmonary exacerbations may allow clinicians to treat pulmonary exacerbations before a large fall in FEV₁ occurs or before a longer time has passed since baseline assessment. To achieve this goal, more aggressive outpatient monitoring or treatment strategies may be required, especially among patients who are at higher risk of failing to recover to baseline.

Our study has several limitations. First, as a retrospective, observational study, we cannot infer causality from the observed associations. In addition, the CFFPR database has several limitations. Data collection and entry are not standardized, and a pulmonary exacerbation can only be defined by the use of IV antibiotics or the selection of a "pulmonary exacerbation" as the indication for hospitalization on the CFFPR encounter form. We therefore could not identify milder exacerbations treated without the use of IV antibiotics. There is no standard definition of a pulmonary exacerbation (2), and it is known that practice patterns vary substantially between US CF Centers (18). That being said, the definition of a pulmonary exacerbation used here has been used in previous studies of CFFPR data (18, 19, 30). The recent CF Foundation guidelines for pulmonary exacerbations (31) recommended that the "restoration of lung function" be one of the goals of treatment, although no specific criterion was given. We chose *a priori* the best FEV₁ in the 6 months before the exacerbation because this goal was thought to be clinically relevant. We chose the best FEV₁ in the 3 months after the exacerbation to ensure there

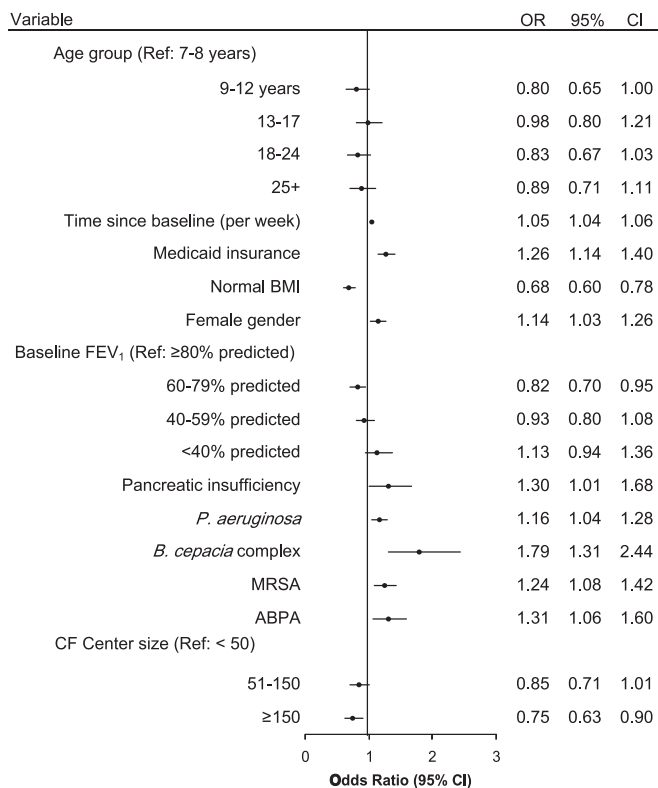


Figure 3. Final model for the failure to recover to baseline FEV₁. The first column lists the variables included in the model. The next column is the estimated odds ratio (OR) and 95% confidence intervals (CI) for the variable. An OR greater than 1 indicates an association with a higher risk of failing to recover to baseline. The next three columns give the estimated OR and 95% CI. A normal BMI is defined as greater than or equal to 18.5 kg/m² for adults or greater than or equal to 5th percentile for children. ABPA = allergic bronchopulmonary aspergillosis; BMI = body mass index; CF = cystic fibrosis; MRSA = methicillin-resistant *Staphylococcus aureus*.

would be adequate FEV₁ measurements available in the database, and to account for any oral or inhaled antibiotics that were administered after completion of IV therapy (but not recorded in the database). When longer periods of follow-up were used (6 and 12 months), lack of response rates continued to be markedly elevated (overall nonresponders at 6 and 12 months: 19% and 15%, respectively). Additionally, our cohort inclusion criteria may have selected sicker patients because they are often seen more frequently. Thus, subjects with insufficient spirometric measurements to be included in our study may have been healthier and be underrepresented in our cohort leading to an overestimation of the proportion of patients that fails to recover to baseline. Rather, subjects included in the study were younger and had better baseline pulmonary function (see Table E6). Subjects with FEV₁ less than 40% predicted may have had fewer measurements of FEV₁ recorded, and thus would be excluded from the study. Additionally, a higher proportion of the subjects included in the study were persistently infected with *P. aeruginosa*. Subjects who were included in the study may have had more respiratory cultures recorded, and thus were more likely to have multiple respiratory cultures that were positive for *P. aeruginosa*. However, a subset analysis of subjects included in the study with at least two respiratory cultures available did not result in changes to the estimated

odds ratios in the final model (data not shown). Because we used a 10% relative difference in FEV₁ (rather than a 10% absolute difference) to determine responder/nonresponder status, our results could have been biased toward patients with poor pulmonary function being more likely to recover to baseline. Conversely, we found that subjects with higher pulmonary function were more likely to recover to baseline. Finally, although we have developed multivariable logistic regression models to address potential confounding, it is possible that residual confounding is present after accounting for these factors. Our models, however, were developed *a priori* after consideration of the available published evidence, a strategy advocated in the statistical literature (32). Additionally, the results of our sensitivity analyses were consistent with the results of our final multivariable logistic regression model.

Despite these limitations, we have shown that 25% of pulmonary exacerbations treated with IV antibiotics result in failure to recover to FEV₁ levels achieved within the 6 months before treatment. We have identified factors associated with the failure to recover to baseline that can be easily assessed by practicing clinicians, allowing us to identify patients who are most at risk for failing to recover to baseline, and providing opportunities for early intervention. Our results suggest that these patients are likely to benefit from closer monitoring, earlier identification, and more aggressive treatment of pulmonary exacerbations. Our results emphasize the need for research into the causes, identification, and treatment of pulmonary exacerbations. The results of this research may lead to a standardized definition and improved treatment approach for pulmonary exacerbations that can prevent the failure to recover to baseline pulmonary function.

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