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Short and long term response to pulmonary exacerbation treatment in cystic fibrosis

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Abstract

Background—Treatment of pulmonary exacerbations (PE_x) in cystic fibrosis (CF) varies widely with no consensus on management practices or best indicators of therapeutic success. To design trials evaluating PE_x treatment factors, we characterize the heterogeneity of PE_x care in adults and pediatrics, and correlate it with measures of clinical response including short and long term lung function changes, change in symptom severity score, and time to next intravenous (IV) antibiotic therapy.

Methods—Data were used from a prospective observational study of CF patients 10 years of age enrolled at six sites between 2007 and 2010. All were started on IV antibiotics for a clinically diagnosed PE_x. ANOVA, logistic and Cox regression were used to examine the association of treatment factors with short and long term clinical response.

Results—Of 123 CF patients (60% female, aged 23.1±10.2 years), 33% experienced <10% relative improvement in FEV₁ during treatment which was associated with failing to recover baseline lung function three months after treatment (OR=7.8, 95% CI=(1.9, 31.6), p=0.004) and a

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longer time to next IV antibiotic (HR=0.48, 95% CI=(0.27, 0.85), p=0.011). Symptom improvement was observed but was not associated with subsequent lung function or time to next antibiotic therapy which had a median recurrence time of 143 days.

Conclusions—Immediate symptomatic or respiratory response to PEx treatment did not have a clear relationship with subsequent outcomes such as lung function or IV antibiotic-free interval. These results can inform future research of treatment regimens for PEx in terms of interventions and outcome measures.

Keywords

cystic fibrosis; pulmonary exacerbation; outcomes

INTRODUCTION

Infection, inflammation, and structural damage of the lung are characteristic of cystic fibrosis (CF). Daily symptoms of chronic infection are punctuated with acute episodes of increased cough, fatigue, physical findings, and other signs including rapid drop in lung function called a pulmonary exacerbation (PEx). Such events are associated with mortality,^{1,2} reduced quality of life,³ unrecoverable loss of lung function,^{2,4} and increased health care costs.⁵ There were over 15,000 PEx recorded in the CF Foundation (CFF) National Patient Registry (NPR) in 2012, affecting nearly 40% of CF patients at least once.⁶ Treatment for PEx varies across patients and centers,⁷ but often includes a combination of intravenous (IV), inhaled, or oral antibiotics⁸ in conjunction with increased airway clearance therapy, inhaled mucolytics, or corticosteroids. Location (inpatient or outpatient) and duration of therapy may differ by factors such as patient gender,^{9,10} age,¹¹ PEx history, disease severity, microbiology, physician goals and patient preferences.¹²

Recent guidelines cite scarce evidence to support common treatment regimens for PEx management,¹³ highlighting the need for research in this area. While studies have examined different short¹⁴⁻¹⁶ and long term^{4,17,18} outcomes of PEx, and factors associated with them, there is no consensus on the most relevant or useful measure of PEx management success - or failure.

Physicians generally treat to alleviate signs and symptoms or recover lost lung function¹⁹ but little is understood about the implications of failing to achieve those immediate goals in CF patients. To inform clinical care and research aimed at improving PEx treatment regimens, we analyzed data from a multi-center, prospective study of PEx to characterize the heterogeneity of treatment factors and correlate them with measures of clinical response, including symptom severity, short and long term lung function, and time to next PEx. Specifically, we aimed to determine the association between immediate symptom and lung function response with subsequent need for IV antibiotics and ultimate pulmonary function recovery.

MATERIALS AND METHODS

Patients and Study Design

CF patients 10 years and older being started on two or more IV antibiotics for a clinically diagnosed PEx using criteria outlined by a CFF Consensus Conference²⁰ were eligible to enroll in the observational study conducted at 6 adult and pediatric CF centers between 2007 and 2010.²¹ Study protocol encouraged at least ten days of antibiotic administration and mucus clearance in accordance with CF Care Guidelines,¹³ but all other treating factors, including location, concomitant administration of inhaled or oral antibiotics or systemic steroids, were at physician's discretion. Spirometry²² and sputum cultures were performed at time of enrollment (within 24 hours of IV initiation) and approximately 10-14 days later. Forced expiratory volume in 1 second (FEV₁) percent predicted of normal was calculated.^{23,24} Participants completed the CF Respiratory Symptom Diary (CFRSD)²⁵ for each day up to 21 days. The study was reviewed and approved by each site's Institutional Review Board, and participant/guardian informed consent/assent was obtained.

Variables and outcomes

The diagnosis of PEx was made by clinician but verified with a scoring algorithm (score excluding change in FEV₁ at admission - 2.6).²⁶ Short term outcomes are those that occur during treatment of the PEx or within 30 days of completion: lung function non-response to treatment was categorized as <10% relative improvement in FEV₁ (L) from enrollment visit (IV antibiotic initiation) to follow-up visit 10-14 days later –within 10 days of end of IV therapy. This represents 'immediate response'¹¹ regardless of a patient's 'baseline' or 'sick decline', and is calculated as a relative change to account for FEV₁ at the time of admission. The Chronic Respiratory Infection Symptom Score (CRISS) was applied to the CFRSD to calculate a severity score from 0-100 (100 being most severe).²⁷ Change in symptom score was calculated from enrollment visit to end of IV therapy or last completed CFRSD (up to 21 days after IV initiation), whichever came first.

Study data were merged with CFFNPR to determine other clinical factors including: CF related diabetes (CFRD), respiratory microbiology, best FEV₁ percent predicted in the preceding 6 months, and history of IV antibiotic episodes in the preceding 6 months. Interim clinical outcomes (those occurring within 3 months of PEx treatment completion) and long term outcomes (those occurring more than 3 months after IV treatment) were also obtained from the CFFNPR. Best FEV₁ percent predicted in the 3 months following study PEx treatment was ascertained to determine 90% recovery of best FEV₁ from 6 months prior⁴ and represents 'baseline recovery'. Time to next IV antibiotic episode (initiated - 7 days after end of IV therapy for study PEx) was calculated, and censored at the time of last encounter.

Statistical Analyses

Summaries including mean and standard deviation (SD) are reported for treatment factors and clinical outcomes by age group (<18 or ≥ 18 years), t-tests and Fisher's exact test compare age groups. Analysis of variance, logistic and Cox regression were used to explore the association of clinical characteristics and treatment factors with symptom response and

FEV₁ change <10% during IV antibiotic treatment, recovery of pre-PEX FEV₁,⁴ and time to next IV antibiotic episode. Backward selection with significance level 0.30 to remain in model was applied to eliminate covariates from the full model which included: female, age 18 years, CFRD, *Pseudomonas aeruginosa* (*Pa*) positive, methicillin-resistant *Staphylococcus aureus* (MRSA) positive, FEV₁ percent predicted <50% at PEX start, 10% drop in FEV₁ percent predicted at initiation of study PEX treatment ('sick decline'), steroid use, oral or inhaled antibiotic use for PEX treatment, MRSA active drug for PEX treatment (doxycycline, linezolid, minocycline, rifampin, tigecycline, vancomycin or trimethoprim/sulfamethoxazole), duration of IV antibiotics (<10 days, 10-14 days, or >14 days), and history of IV antibiotics in the preceding 6 months. A relaxed 0.30 criteria was used to allow non-significant covariates in the model which stabilize estimates of other parameters.²⁸ Immediate lung function non-response (<10% relative improvement in FEV₁ (L) during treatment) and change in symptom score²⁷ were then added to the models for (1) failure to recover baseline FEV₁(2) time to next IV antibiotic. Model coefficient estimates including odds ratios (OR) and hazard ratios (HR) are reported with 95% confidence intervals (CIs). Reported p-values are two sided and considered exploratory; no adjustments were made for multiple comparisons. No sample size estimates were performed. Analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, NC, 2009), and R (version 2.15, The R Foundation for Statistical Computing, Vienna, Austria, 2012).

RESULTS

A total of 123 CF patients (60.2% female) were treated with IV antibiotics for a diagnosed PEX (Table 1). Average age was 23.1 years (SD=10.2) and FEV₁ percent predicted (%) at admission was 55.8% (SD=20.9). Pediatric patients (10 -17 years old) made up 35% (n=43) of the cohort, and best FEV₁ in 6 months prior was on average (SD) 83.1% (18.3) in children and 53.2% (19.7) in adults. *Pa* was more prevalent in adults (75.0% versus 44.2%, p=0.001), while MSSA (28.8% versus 27.9%, p=0.9) and MRSA (28.8% versus 39.5%, p=0.23) were similar in adults and children.

PEX Treatment

PEX treatment features are in Table 2 by age. None of the pediatric patients were treated exclusively at home and adults were treated on average 4.2 days longer than those under 18 years (95% CI=(1.5, 6.9), p=0.003). IV tobramycin was the most commonly prescribed antibiotic in combination; pediatric patients were more likely to get a MRSA active antibiotic (65.1% versus 45.0%, p=0.039), and 16.3% overall received systemic corticosteroids.

PEX Outcomes

Supplementary Figure 1 shows enrollment and follow-up for each of the outcomes. Table 3 summarizes short and long term clinical outcomes by age group. Among the 102 participants with spirometry at enrollment and at or near the end of IV antibiotic treatment, 73% had lung function measured within ± 2 days of IV end, 93% were within a week; 2 had PFTs not within 10 days of IV end and were removed from the calculations. There was marked improvement in immediate FEV₁ response in the younger patients (5.9% predicted

more than adults, 95% CI=(2.3, 9.5), $p=0.002$) (Figure 1), while both age groups had similar response in symptom severity, baseline FEV₁ recovery in subsequent 3 months, and IV antibiotic need (by 30, 90 and 180 days) after treatment for study PEX. The Kaplan-Meier curves (Figure 2) for time to next IV antibiotic did not significantly differ by age group (p -value=0.74).

Association of demographic, clinical, and treatment factors with outcomes

Figure 3 shows the association of clinical and treatment factors with each of the clinical responses ($p<0.30$). MRSA was associated with a diminished symptom severity reduction (average 8.8 point increase, 95% CI=(1.8, 15.8), p -value= 0.015), while treatment choices such as steroids (-12.0 points, 95% CI=(-19.7, -4.3), p -value= 0.003), oral/inhaled antibiotics, and MRSA active drugs were associated with larger reductions in symptom severity. Longer treatment durations (10-14 days and >14 days as compared to <10 days) were associated with less symptom improvement but not statistically significant.

Immediate FEV₁ non-response was associated with use of oral/inhaled antibiotics (OR=3.5, 95% CI=(1.2, 10.6), p -value=0.027) and longer treatment duration (>14 days compared to <10 days, p -value=0.021), whereas a drop of 10% FEV₁ at admission had a protective effect and was associated with a *reduced* odds of failure to recover (OR=0.30, 95% CI=(0.11, 0.81), p -value=0.017). CFRD was the only covariate with a common, though weak, association with both immediate FEV₁ response (p -value=0.221) and recovery of baseline FEV₁ (p -value=0.257). History of IV antibiotics was the only factor significantly associated (OR=4.8, 95% CI=(1.2, 18.4), $p=0.023$) with non-recovery of baseline FEV₁ post treatment.

The hazard of subsequent IV antibiotic was significantly increased by history of IV episodes (HR=2.7, 95% CI=(1.8, 4.1), p -value<0.001) and low FEV₁ at admission (HR=2.4, 95% CI=(1.5, 3.9), p -value<0.001), whereas longer treatment duration was associated with a reduced time to next exacerbation (10-14 days: HR=0.50, 95% CI=(0.29, 0.889), p -value=0.018; >14 days: HR=0.38, 95% CI=(0.20, 0.70), p -value=0.002).

Short term response and subsequent outcomes

Change in symptom score was not associated with recovery of baseline lung function (p -value =0.49) or time to next IV antibiotic (p -value= 0.69) when added to the multivariate logistic and Cox regression models presented in Figure 3 and Supplementary Table 1, respectively. Immediate non-response in FEV₁ (<10% during treatment) significantly increased the odds of non-recovery of baseline (OR=7.8, 95% CI=(1.9, 31.6), p -value =0.004); no other covariates were significantly associated with post-PEX recovery when adjusted for short term FEV₁ response. Among those with immediate FEV₁ response, 95% recovered baseline by 3 months, whereas among those who had <10% improvement during treatment, 73% recovered baseline. Figure 4 shows lung function by short term FEV₁ responder status.

In contradiction, short term FEV₁ non-response significantly decreased the risk of subsequent IV antibiotic event (HR=0.48, 95% CI=(0.27, 0.85), p -value=0.011) along with other significant factors that increased the risk: being female (HR=1.8, 95% CI=(1.1, 3.1), p -

value=0.032), history of IV antibiotic event (HR=2.8, 95%CI=(1.6, 4.8), p-value<0.001), and low FEV₁ at start of study PEx (HR=2.0, 95%CI=(1.2, 3.4), p-value=0.01). Figure 5 shows the Kaplan-Meier curves to next IV antibiotic episode by short term FEV₁ responder status (p-value= 0.07).

DISCUSSION

CF pulmonary exacerbations are managed with a wide array of treatment regimens that may be based on patient or clinician preference, pathogen isolation, historical response, or trajectory of response to treatment for the current PEx. In general, the short term goals of treatment are to resolve symptoms and recover lost lung function, but there may also be long term goals, such as preservation of lung function and prevention of subsequent acute events. We show, across multiple centers, that patient clinical characteristics and treatment factors that were associated with short term clinical improvement differed from those associated with subsequent lung function recovery and time to next acute event treated with IV antibiotics. In addition, immediate symptom resolution and lung function response did not have a clear relationship with longer term clinical outcomes.

To our knowledge, this is the first study to examine the multi-factorial association between clinical and treatment features with patient reported symptoms during a pulmonary exacerbation. Improvement (i.e. reduction in symptom score) was seen in nearly all patients; however presence of MRSA was related to a diminished effect while steroids were significantly associated with a greater effect. This is contrary to a small randomized trial of steroids in CF children that failed to see an effect of steroids on symptoms.²⁹ Treating to improve patient signs and symptoms is a hallmark component of PEx management; however it may not be indicative of downstream clinical outcomes. A CF symptom score during PEx³⁰ has been associated with extending IV antibiotic duration¹⁷ and time to next PEx,³¹ but not when adjusting for other factors –similar to the findings of this study. The antibiotic course may be extended because of seeming lack of symptom improvement but it is unclear if there are advantages to longer treatment that outweigh cost, time, and potential toxicities.

The other common goal of PEx treatment is recovery of lost lung function. Nearly 90% of this sample recovered baseline lung function –higher than the 75% observed in the Registry from 2003-2006.⁴ We found that failure to improve FEV₁ during treatment was associated with failure to recover pre-PEx lung function in the subsequent three months; however, in contradiction short term FEV₁ non-response was associated with longer time to next IV antibiotic episode. Perhaps the patients with the highly variable, oscillating swings in lung function –large drops and big gains with treatment are easier to identify as requiring treatment for exacerbation,³² while those who are less responsive to IV antibiotics may be less likely to be admitted again for IV treatment when it didn't appear to improve the patient's lung function. This analysis specifically examined the association of relative FEV₁ improvement during treatment for PEx and subsequent 'baseline recovery' while adjusting for 'sick decline' and lung function at admission. An alternative short term metric would be recovery of baseline lung function (best 6 months prior) at the end of treatment; however such a measure would confound 'sick decline' rather than letting the analysis tease out any effect. Also, the calculation of baseline recovery includes the FEV₁ measured at end of

treatment (which is often the highest in the 3 months post IV therapy); these measures of 'immediate response' and 'recovery of baseline' guaranteed mutually exclusive endpoints.

Extending the PEx free interval is an important feature of CF disease management because these acute events have been shown to have long term detrimental effects.^{1,18,33} For this reason, time to next IV antibiotic course or PEx is a common and useful endpoint in clinical trials of chronic therapies;^{34,35} however it could be argued that because the majority of these events occur 4-6 months after treatment, they are too far downstream and confounded by factors not related to the acute management of the preceding PEx to serve as useful outcomes when studying success or failure PEx treatment regimens. Similarly, long term lung function decline has been explored within the context of PEx; however for studying PEx treatment regimens, an immediate outcome is necessary for both practicality and to reduce the influence of confounding factors. Several have shown the detrimental effect of exacerbation on long term lung function in CF.^{4,18} These study data support those findings (history of IV antibiotics significantly increased the risk of failing to recover baseline lung function) and likely demonstrate that recurrent PEx events and underlying phenotype such as CFRD and MRSA colonization are responsible for persistent respiratory decline more than a particular treatment regimen or response.

The inclusion criteria of this study required dual systemic, intravenous antibiotic therapy and thus likely excluded patients treated solely for MRSA infection (either because of exclusively oral or mono-therapeutic choices). Thereby; inference here applies only to CF exacerbations that required systemic dual therapy. The PEx guidelines found insufficient evidence to necessitate two antibiotics when *Pa* is suspected; but neither was there support for less than two, and thus yielded to standard practice of two.¹³ *Pa* prevalence in this study is consistent with the general CF population.⁶ PEx treatment guidelines also cited insufficient evidence of either benefit or harm from acute steroid use to treat CF exacerbations.¹³ While this study found some moderate benefit from steroid use, interpretations should be exercised with caution because of the potential for indication bias in a non-randomized study. The question of acute corticosteroids for treating CF PEx is of tremendous interest and would benefit from carefully controlled, randomized research.

There were limitations to our analysis of this observational study, one being that treatments may have been proxy for baseline clinical features or confounded with response. For example, duration was a treatment factor in this analysis; however antibiotic regimens often changed and extended mid-course presumably for reasons of clinical non-response, therefore treatment was confounded with outcomes and has been treated as such in other studies.^{15,17} Additions or changes to the treatment may have been related to microbial susceptibility testing, or convenience/preference. For these reasons it is challenging to interpret the relationship between treatment factors and outcomes. This multi-site pediatric and adult study augmented with CF NPR data yields generalizable findings for short and long term PEx outcomes –perhaps at the expense of increased heterogeneity resulting from site variability, irregular spirometry timing, and unmonitored supplemental data. Lastly, all our statistical models were estimable and coefficients were stable; however the sample size is moderately small and no adjustments were made for multiple comparisons, therefore associations and p-values should be interpreted with caution.

Symptom resolution and immediate improvement in FEV₁ are meaningful measures of acute PEx therapy, and we show them to be more associated with treatment features than long term measures. Short term non-response in symptoms or lung function during treatment was not clearly related with subsequent PEx; however immediate FEV₁ response does appear to be associated with recovery of baseline lung function. Also, some of the contradictory results we observed support the use of a composite response¹⁵ of short term clinical features to serve as a trial outcome (e.g. lung function or symptom improvement without additional IV antibiotics within a month of the initial treatment). A larger cohort may support or refute our results, while randomized controlled studies of PEx treatment will ultimately produce the evidence necessary to improve the overall wellbeing of patients with CF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is the key question?

How do varying treatments for pulmonary exacerbation in CF correspond with clinical response, including symptom severity, short and long term lung function, and time to next PEx?

What is the bottom line? Across multiple centers, the patient clinical characteristics and treatment factors that are associated with short term clinical improvement differ from those associated with subsequent lung function recovery and time to next acute event treated with IV antibiotics.

Why read on? This is the only multi-center evaluation of clinically-defined pulmonary exacerbations in both pediatric and adult CF patients to examine a comprehensive set of clinical responses for determining an outcome measure for future studies of exacerbation therapies.

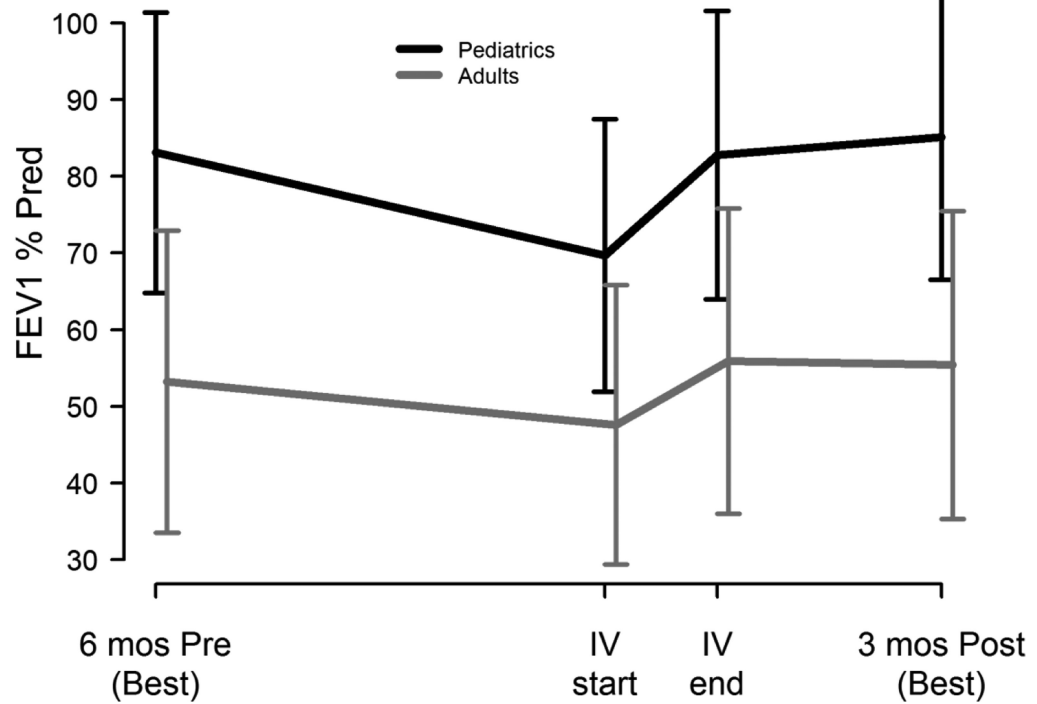


Figure 1. Lung function by age group

FEV1 % of predicted mean \pm 1SD for pediatric participants (black lines, n=37) and adult participants (gray lines, n=71): best during 6 months before study PEx, at time of IV initiation for PEx, at end of IV for PEx, and best during 3 months after study PEx.

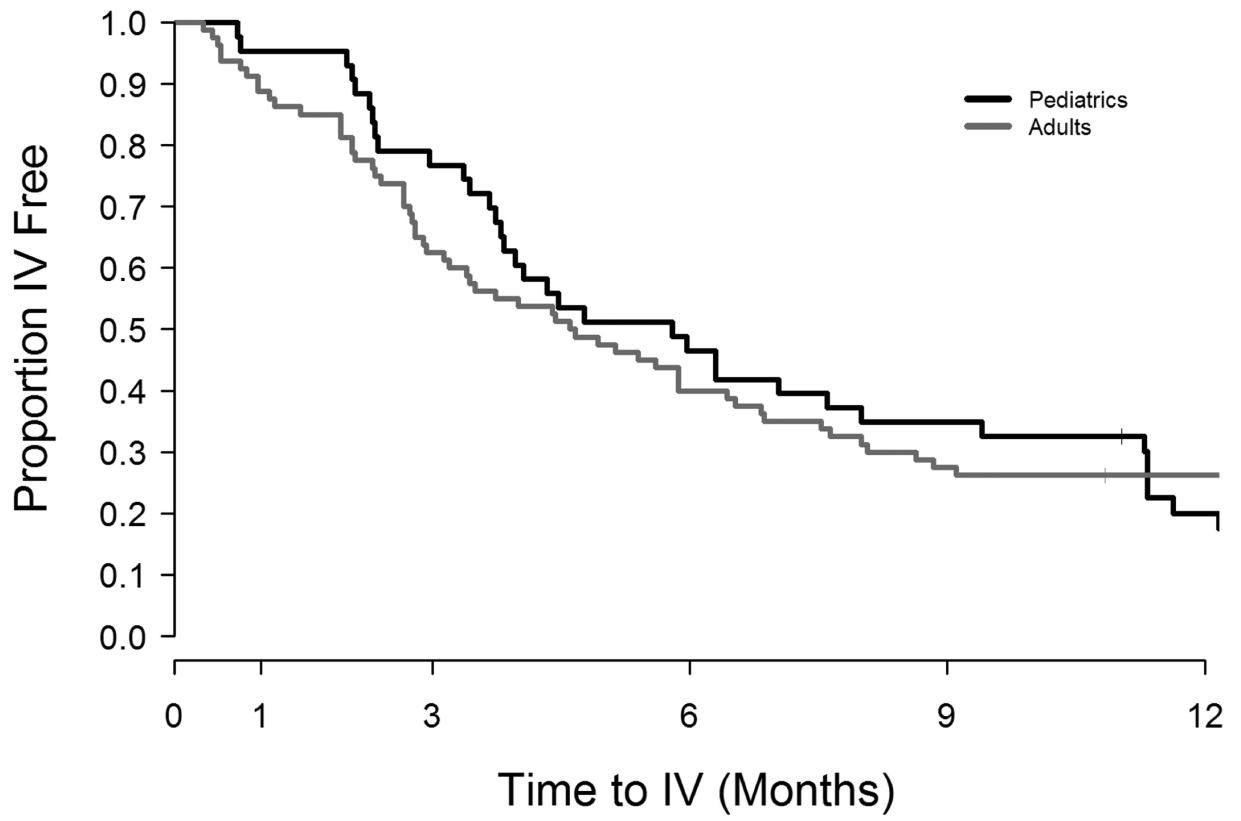


Figure 2. Kaplan-Meier survival curves for time to next IV antibiotic episode by age group
Proportion IV antibiotic free by time (after study PEx) in pediatric (black lines, n=43) and adult participants (gray lines, n=80).

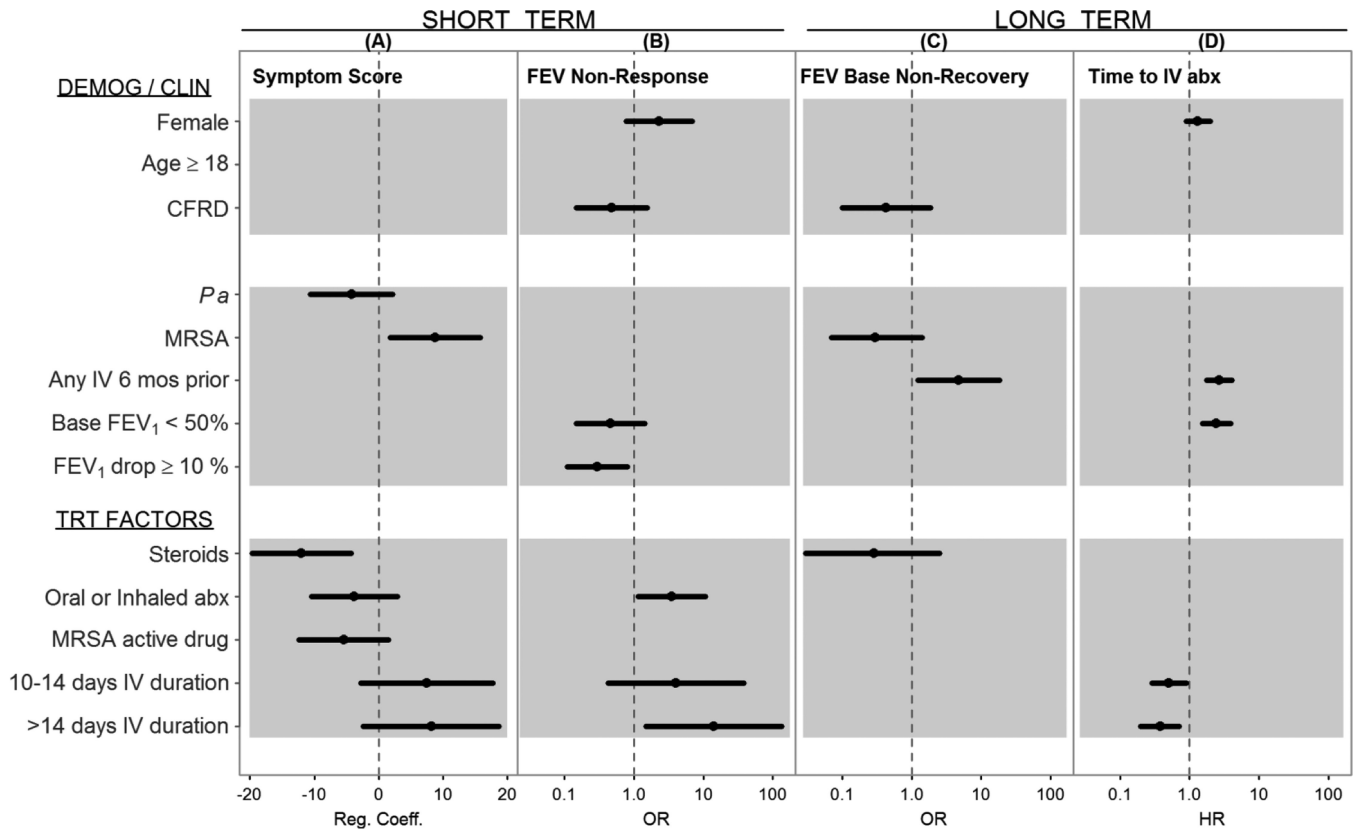


Figure 3. Factors associated with short and long term outcomes of PEx treatment
(A) Multivariate regression coefficients (Reg. Coeff) and 95% CIs for demographic (DEMOG), clinical (CLIN) and treatment (TRT) factors associated with CRISS symptom score (- is an improvement). **(B)** Multivariate odds ratios (OR) and 95% CIs for factors associated with <10% immediate response in FEV₁ (L) during treatment. **(C)** Multivariate ORs and 95% CIs for factors associated with <90% baseline (Base.) FEV₁ recovery. **(D)** Multivariate hazard ratios (HR) and 95% CIs for factors associated with time to next IV antibiotic (abx). Factors with p-value <0.30 were dropped from model and not estimated or plotted in figure. CFRD=cystic fibrosis related diabetes; *Pa*=*P. aeruginosa* colonized at time of PEx; MRSA=colonized at time of PEx; Base FEV₁ (<50%)=FEV₁ percent predicted at time of PEx; FEV₁ Drop= FEV₁ drop ≥ 10% presenting for PEx; Oral or Inh=Use of oral or inhaled antibiotics during treatment for PEx; MRSA active drug= use of doxycycline, linezolid, minocycline, rifampin, tigecycline, vancomycin or trimethoprim/sulfamethoxazole; 10-14 Days= total duration of IV antibiotic therapy compared to reference <10 Days; >14 Days=total duration of IV antibiotic therapy compared to reference <10 Days.

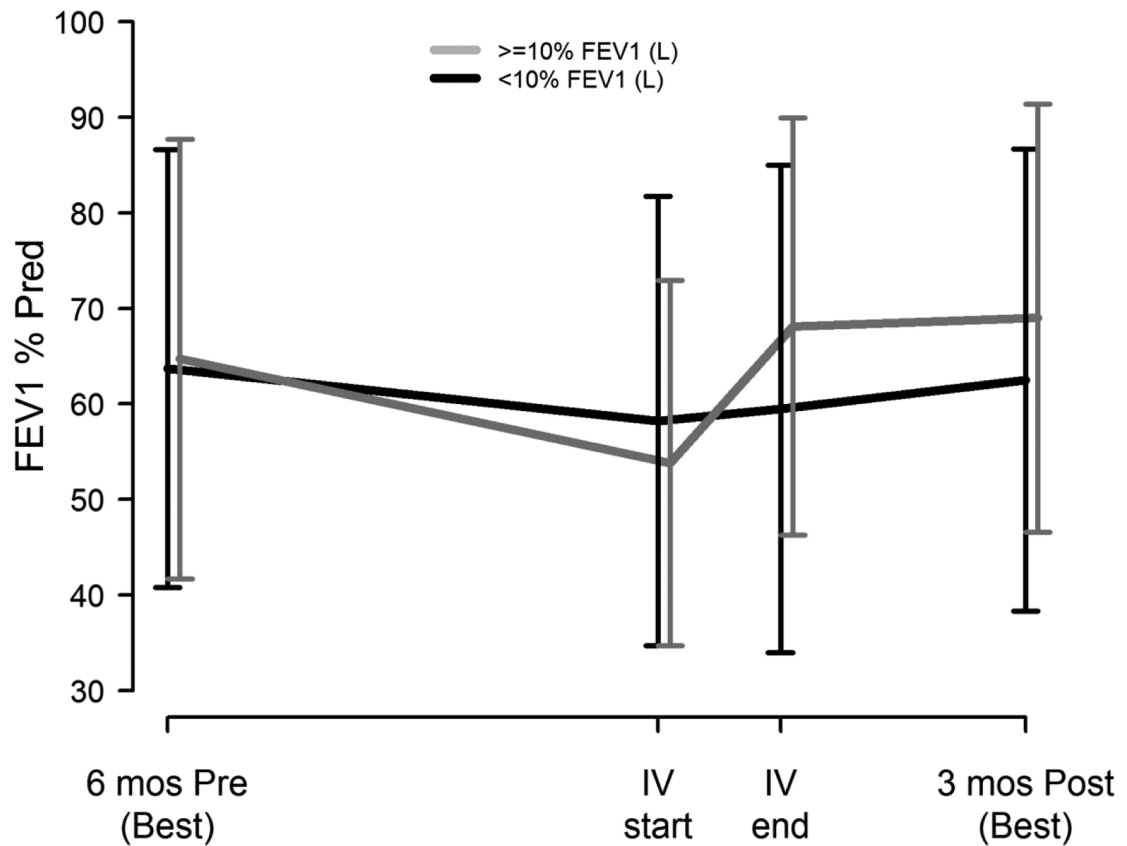


Figure 4. Lung function by immediate FEV₁ response with treatment

FEV₁ % of predicted mean \pm 1SD for participants with $< 10\%$ relative FEV₁ (L) response during PEx treatment (black lines, n=35) and participants $\geq 10\%$ relative FEV₁ (L) response during treatment (gray lines, n=67): best during 6 months before study PEx, at time of IV initiation for PEx, at end of IV for PEx, and best during 3 months after study PEx.

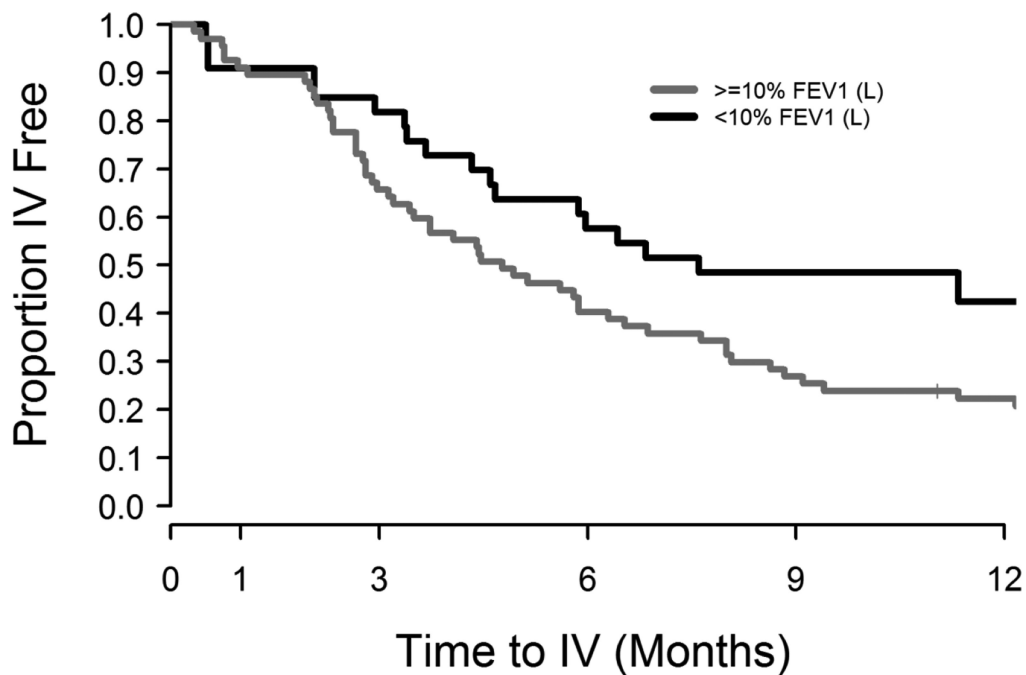


Figure 5. Kaplan-Meier survival curves for time to next IV antibiotic episode by immediate FEV₁ response with treatment
 Proportion IV antibiotic free by time (after study PEx) in participants with <10% relative FEV₁ (L) response during PEx treatment (black lines, n=35) and those with ≥10% relative FEV₁ (L) response during treatment (gray lines, n=67).

Table 1

Demographics and Baseline Characteristics

Study Participants (N=123)		
	N	%
Sex -Female	74	60.2
Race		
Caucasian	114	92.7
Hispanic	3	2.4
African-American	4	3.3
Asian	1	0.8
Pacific Islander	1	0.8
Genotype		
Delta F508 Homozygous	67	54.5
Delta F508 Heterozygous	45	36.6
Other/Unknown/ Not genotyped	11	8.9
Pancreatic insufficient^[1]	117	95.1
Age Group		
10-17 yrs	43	35.0
18 yrs	80	65.0
FEV₁ % Predicted^[2]		
<50%	49	39.8
50%-69%	34	27.6
70%-89%	26	21.1
90%	7	5.7
FEV₁ drop 10% predicted presenting for PE^[3]	66	53.7
IV abx for PE in 6 months prior^[4]	51	41.5
Microbiology^[5]		
<i>Pa</i>	79	64.2
MSSA	34	27.6
MRSA	40	32.5
<i>B. cepacia</i>	4	3.3
<i>S. maltophilia</i>	15	12.2
<i>A. xylosoxidans</i>	11	8.9
<i>H. influenza</i>	4	3.3
Aspergillus	9	7.3
CF Related Diabetes	37	30.1
	Mean	SD
Age (years)	23.1	10.2

Study Participants (N=123)		
	N	%
Body Mass Index (kg/m²)	19.9	3.4
FEV₁ % Predicted at enrollment^[2]	55.8	20.9
FEV₁ % Best in 6 months prior to visit 1^[6]	63.7	23.9

[1] Evidence of pancreatic enzyme use

[2] Spirometry % predicted is calculated using the Wang equations²⁴ for females less than 16 years of age and males less than 18 years of age. The Hankinson equations²³ are used for females 16 years and older, males 18 years and older

[3] As reported as criterion on pulmonary exacerbation diagnostic form

[4] One or more episodes of IV antibiotic for reason “pulmonary exacerbation” recorded in the CFF Registry in 6 months prior to study PEx

[5] Among respiratory cultures isolated at time of enrollment (n=107) or in CFF registry in 6 months prior to enrollment (n= 16). *Pseudomonas aeruginosa* (Pa), *Methicillin-sensitive Staphylococcus aureus* (MSSA), *Methicillin-resistant Staphylococcus aureus* (MRSA), *Burkholderia* (B.), *Stenotrophomonas* (S.), *Achromobacter* (A.), *Haemophilus* (H.)

[6] Best of all spirometry in CFF Registry in 6 months prior to study PEx

Table 2

Pulmonary exacerbation treatment by age group

	Age Group		
	< 18 years N=43	18years N=80	All N=123
Duration of IV antibiotics mean (SD) n (%)	14.0 (5.6)	18.2 (9.8)	16.7 (8.8)
0-10 days	11 (25.6)	9 (11.3)	20 (16.3)
>10-14 days	21 (48.8)	26 (32.5)	47 (38.2)
>14-21 days	8 (18.6)	31 (38.8)	39 (31.7)
>21 days	3 (7.0)	14 (17.5)	17 (13.8)
Location of Treatment n(%)			
Exclusively hospital	28 (65.1)	35 (43.8)	63 (51.2)
Exclusively home	0 (0)	21 (26.3)	21 (17.1)
Both hospital and home	13 (30.2)	23 (28.8)	36 (29.3)
Unknown	2 (4.7)	1 (1.3)	3 (2.4)
Number of IV Antibiotics n(%)			
1	1 (2.3)	1 (1.3)	2 (1.6)
2	23 (53.5)	46 (57.5)	69 (56.1)
3	16 (37.2)	25 (31.3)	41 (33.3)
4+	3 (7.0)	8 (10.0)	11 (8.9)
Most common IV antibiotics n(%)			
Tobramycin	22 (51.2)	54 (67.5)	76 (61.8)
Meropenem	12 (27.9)	45 (56.3)	57 (46.3)
Ceftazidime	7 (16.3)	27 (33.8)	34 (27.6)
Vancomycin	18 (41.9)	11 (13.8)	29 (23.6)
Cefepime	11 (25.6)	12 (15.0)	23 (18.7)
MRSA^[1] active drug n(%)	28 (65.1)	36 (45.0)	64 (53.0)
Inhaled Antibiotics n(%)	5 (11.6)	7 (8.8)	12 (9.8)
Oral Antibiotics n(%)	5 (11.6)	22 (27.5)	27 (22.0)
Steroids n(%)	7 (16.3)	13 (16.3)	20 (16.3)

^[1]Received any of: doxycycline, linezolid, minocycline, rifampin, tigecycline, trimethoprim/sulfamethoxazole, or vancomycin

Table 3

Clinical Response by age group and overall

		Age Group		Total N=123
		< 18 N=43	18 N=80	
Short Term Treatment Response				
Improvement in symptom score ^[1]	n	36	57	93
	mean (SD)	-21.7 (13.9)	-22.2 (14.9)	-22.0 (14.4)
Change in FEV ₁ (% predicted) ^[2]	n	35	65	100
	mean (SD)	13.9 (9.2)	8.0 (8.3)	10.0 (9.1)
< 10% improvement FEV ₁ (L) ^[3]	n (%)	10 (28.6)	23 (35.4)	33 (33.0)
IV antibiotic within 30 days of completing IV for study PE ^[4]	n (%)	2 (4.7)	9 (11.3)	11 (8.9)
Interim Response: 3 months post study PE				
Change in best FEV ₁ (% predicted) from 6 mos prior to 3 mos post PE	n	37	71	108
	mean (SD)	1.6 (12.4)	2.5 (7.9)	2.2 (9.6)
< 90% FEV ₁ baseline recovery ^[5]	n (%)	5 (13.5)	8 (11.3)	13 (12.0)
IV antibiotic within 90 days of completing IV for study PE ^[4]	n (%)	10 (23.3)	30 (37.5)	40 (32.5)
Long Term Response:				
IV antibiotic within 180 days of completing IV for study PE	n (%)	23 (53.5)	48 (60.0)	71 (57.7)
Time to next IV antibiotic ^[4] (days)	mean (SD)	236.5 (190.3)	234.7 (235.9)	235.3 (220.2)
	median	174.0	139.0	143.0
	min, Max	22.0, 740.0	10.0, 984.0	10.0, 984.0

[1] Improvement in CF Respiratory Infection Symptom Score (CRISS) during treatment for study PE

[2] Absolute change in percent predicted during study PE treatment from visit 1 to visit 2

[3] <10% relative change in FEV₁ (L) during study PE treatment (N=100, n<18=35, n 18=65)

[4] Only IV antibiotic episodes occurring 7 or more days after end of treatment for study PE are considered

[5] Best FEV₁ (% predicted) 3 months post study PE < 0.90 of best FEV₁ (% predicted) 6 months prior to study PE⁴ (N=108, n<18=37, n 18=71)