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Journal of Cystic Fibrosis 17 (2018) 760–768

www.elsevier.com/locate/jcf

Original Article

Characteristics and outcomes of oral antibiotic treated pulmonary exacerbations in children with cystic fibrosis☆

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Received 4 April 2018; revised 25 May 2018; accepted 29 May 2018
Available online 18 June 2018

Abstract

Background: Pulmonary exacerbations (PEx) in children with cystic fibrosis (CF) are frequently treated in the outpatient setting with oral antibiotics. However, little is known about the characteristics of PEx managed on an outpatient basis and the effectiveness of oral antibiotic therapy. We sought to prospectively evaluate clinical and laboratory changes associated with oral antibiotic treatment for PEx.
Methods: Children with CF between 8 and 18 years of age prescribed two weeks of oral antibiotics for a PEx were eligible to enroll. The study consisted of a visit within 48 h of starting antibiotics and a second visit within one week of antibiotic completion. Twenty-eight participants were evaluated by exacerbation score, quality of life measurements, lung function, sputum microbiology and inflammation.
Results: Oral antibiotic treatment was associated with a significant improvement in exacerbation score and quality of life measured by the CF Questionnaire-Revised (CFQ-R) respiratory domain. Following treatment, forced expiratory volume in 1 s (FEV_1) % predicted increased [median (range)] 9% (−8%, 31%), and 22 (81%) subjects returned to 90% or higher of baseline FEV_1. Bacterial density of the primary organism identified on sputum culture decreased significantly with a median (range) decrease of 0.8 $\log_{10}$ cfu/mL (−8 $\log_{10}$, 2 $\log_{10}$, $p = 0.03$). Sputum neutrophil elastase [−37 μg/mL (−464, 272), $p = 0.02$] and IL-1β [-2.8×10^3μg/mL (-6.9×10^4, 3.3×10^4), $p = 0.03$] decreased significantly following treatment in this cohort.
Conclusions: Treatment of PEx with oral antibiotics was associated with measurable improvements in patient reported outcomes, lung function, bacterial density and sputum inflammatory markers.
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Keywords: Cystic fibrosis; Pulmonary exacerbation; Lung function; Inflammation; Infection

1. Introduction

Pulmonary exacerbations (PEx) are a frequent occurrence in cystic fibrosis (CF) and are characterized by a constellation of symptoms including increased cough, increased sputum production and decreased exercise tolerance [1]. PEx are frequently treated in the outpatient setting with oral antibiotics, especially in younger patients and those with preserved lung function [2]. However, despite the routine use of oral antibiotics to treat symptoms of a PEx, there are limited data available describing the clinical and laboratory changes that occur with the onset of these PEx

Abbreviations: PEx, Pulmonary exacerbation; NE, Neutrophil elastase; HMGB, Human mobility group box; PES, Pulmonary exacerbation score

☆ Preliminary data was presented as an abstract at the 2016 North American Cystic Fibrosis Conference in Orlando, Florida on October 27th, 2016.

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https://doi.org/10.1016/j.jcf.2018.05.015
1569-1993Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society.

and subsequent oral antibiotic treatment [2–4]. Multiple studies examining clinical outcomes with intravenous (IV) antibiotic treatment of PEx have been performed [5–7]. However, the results of these studies may not be generalizable to PEx treated with oral antibiotics.

There are key gaps in our knowledge related to oral antibiotic treatment of PEx in pediatric patients with CF including changes in clinical outcomes, recovery of lung function, and alterations in bacterial density and measures of airway inflammation [8]. Therefore, we sought to prospectively determine changes in patient reported outcomes, lung function, airway infection and inflammation in a cohort of school aged children with CF treated for a PEx with oral antibiotics in the outpatient setting.

2. Methods

2.1. Study population and design

Subjects between the ages of 8 and 18 years with a diagnosis of CF based on a sweat chloride ≥60 mEq/L and/or the presence of two known CFTR mutations who met criteria for a PEx [9] and were prescribed oral antibiotics as treatment were eligible to enroll. Individuals met criteria for a pulmonary exacerbation with a score of 5 or higher (out of 16 possible points) based on symptoms over the prior two weeks and physical exam findings [9]. Scoring was based on assessment of the following: worsening cough, sputum production, chest tightness, exercise tolerance, missed school or work and new auscultatory findings on chest exam. Subjects were excluded from participation if their FEV_1 was <40% predicted, if they were receiving chronic oral antibiotics, had received oral or IV antibiotics within the prior two weeks, or were being simultaneously started on inhaled antibiotics. Those who were receiving inhaled antibiotics as part of their chronic management were eligible to enroll if inhaled antibiotics were continued as previously scheduled. Those receiving chronic thrice weekly azithromycin were also eligible to enroll. Subjects were only eligible to participate in the study once and could not be re-enrolled with a second exacerbation. Subjects were recruited either in the CF clinic at the time of an antibiotic prescription or by phone if a subject's primary CF provider prescribed antibiotics based on telephone triage.

The study consisted of a visit within 48 h of starting antibiotics and a second visit within one week of antibiotic completion. All patients received a two-week course of oral antibiotics. Antibiotic choice was determined by the primary CF provider, using our CF Center's standardized approach for antibiotic selection based on prior respiratory culture results. Demographic information including age, gender, race and medical history (genotype, CF comorbidities, medications) were recorded. Pulmonary function testing was performed pre- and post-bronchodilator at each research visit. Baseline lung function measurements, defined by the highest FEV_1 value in the prior six months, were compared to pre-bronchodilator values at PEx onset and the end of antibiotics. The results of pulmonary function tests for the 6 months following an exacerbation were also captured and the highest FEV_1 during this time frame was compared to post-antibiotic values. A sputum sample, either expectorated or induced, was obtained for assessment of infection and inflammation (see next section for further details). Viral testing of sputum by a multiplex polymerase chain reaction (PCR) panel of 8 viruses was performed at the first visit (see next section for additional details). A Pulmonary Exacerbation Score (PES) was obtained at each visit [9]. Quality of life measurements were assessed using the CF Questionnaire-Revised. The Colorado Multiple Institutional Review Board approved this study. Informed consent and assent, when appropriate, was obtained from all patients. HIPAA standards were maintained during this study.

2.2. Assessment of airway infection and inflammation

Two sputum samples at visit 1 and 2 were collected from each patient. If a subject was unable to expectorate, sputum induction was performed in a dedicated clinic room according to a standard operating procedure as previously published [10]. One sample was sent to the clinical microbiology lab, processed and underwent comprehensive examination for CF bacterial and fungal pathogens per CF consensus guidelines [11]. Additionally, this sputum sample was tested for viruses using respiratory virus PCR (Luminex Molecular Diagnostics X-tag RVP). This assay will detect the following viruses: influenza A/B, human metapneumovirus, respiratory syncytial virus, parainfluenza, adenovirus, coronavirus and rhinovirus/enterovirus. The second sample was sent to the Pediatric Clinical Translational Research Center Core Laboratory at Children's Hospital Colorado and processed using a standard operating procedure [10] for cytology (including total cell counts and neutrophils) and measurement of the following inflammatory markers: free neutrophil elastase (NE) activity, human mobility group box (HMGB)-1, interleukin (IL)-8 and IL-1β. Criteria for sputum acceptability can be found in the online supplement. Sputum cytology was performed in a subset of these samples (n = 9) when immediate processing within 30 min of collection was possible. NE activity was quantified by a spectrophotometric assay based on the hydrolysis of the specific substrate MeO-suc-Ala-Ala-Pro-Ala-*p*-nitroanilide (Sigma Chemical Co, St. Louis, MO). IL-8 and IL-1β were quantified on a Luminex multiplex platform using commercially available reagents (R&D Systems, Minneapolis, MN). HMGB-1 was measured using an enzyme-linked immunosorbent assay (IBL International, Morrisville, NC). The lower limits of detection for these assays were: NE activity, 0.5 μg/mL; IL-1β, 0.34 pg/mL; IL-8, 0.78 pg/mL; HMGB-1, 0.6 ng/mL.

2.3. Statistical analysis

The study was powered on the expected reduction of bacterial density, assuming that the bacterial colony count would be reduced to a lesser degree with oral antibiotics than IV treatment [7]. With a sample size of 30 subjects, a mean change in bacterial density of 1.5 $\log_{10}$ cfu/mL (colony forming units) could be detected with 80% power and a significance level of 0.05. The dominant bacterial pathogen, defined as the bacterium isolated in the highest concentration in the first

sputum culture, was used to assess for the reduction in bacterial density. The bacterial density was log transformed prior to performing statistical analyses. Signed rank tests were used to compare variables before and following a two week antibiotic course. Lung function (a secondary outcome) was calculated using the Global Lung Initiative equations [12] and evaluated at multiple time points using a repeated measures ANOVA. A lasso regression model was fit to the percent FEV_1 recovery variable to identify predictors of recovery defined as an FEV_1 within 90% of baseline. Eligible variables for the model were gender, FEV_1% predicted at start of PEx, PES, age, negative viral PCR, negative CF pathogen culture, positive bacterial culture for *Pseudomonas aeruginosa* and F508del mutation. Since percent recovery and drop in FEV_1 from baseline are both functions of the same FEV1 value (baseline), they are highly correlated (see Supplemental Fig. 1). For this reason, we opted to include the FEV_1 value at the PEx onset since this value was not included in the percent recovery calculation and would therefore not be effected by spurious correlation.

3. Results

3.1. Demographics and treatment adherence

Thirty-two children with CF were enrolled in the study. Two subjects withdrew prior to completing visit 1, one subject did not return for the second study visit, and one subject was withdrawn from the study due to new growth of *P. aeruginosa* and initiation of inhaled antibiotics. Demographic information and clinical characteristics for the subjects that completed both visits (n = 28) are listed in Table 1. This table captures baseline (prior to the onset of PEx) and visit 1 data. The genotype distribution and average lung function in this cohort generally reflect those in our overall pediatric population. The changes in clinical and laboratory outcomes with oral antibiotic treatment for this cohort are described in Table 2

Twenty-six out of 28 subjects completed a diary tracking timing of antibiotic doses and airway clearance. These subjects performed a mean of 27 airway clearance treatments (range: 13–42) over the two-week period, averaging 1.9 airway clearance treatments per day. Over the two-week period, subjects reported missing an average of less than one antibiotic dose (range: 0–5).

3.2. Changes in patient reported symptoms and outcomes

The median baseline pulmonary exacerbation score (PES) was 6 with a range of 5–16 (n = 27). The median change in PES following completion of oral antibiotics was −6 (−16, 2 $p < 0.01$) (Supplemental Fig. 2). A significant improvement in the respiratory domain of the CFQ-R was observed in both patient and parent reported questionnaires (Supplemental Fig. 3). The patient respiratory domain score had a median (range) improvement of 16.7 (−5.6, 66.7, $p < 0.01$) post-antibiotics compared to the pre-antibiotic score. The parent reported respiratory domain score had a median improvement of 22.2 (0, 72.2, $p < 0.01$) following antibiotics. There were no significant changes in the other domains of the CFQ-R (physical, emotion, body image, eating, treatment burden and digestive).

Table 1
Patient characteristics at baseline and pulmonary exacerbation onset.

	N = 28
Female: Male	11:17
Age in years, median (range)	14 (8–18)
Genotype, N (%)	
F508del/F508del	17 (61%)
F508del/other	9 (32%)
Other/other or missing	2 (7%)
Baseline FEV_1% (highest predicted in prior 6 months), median (range) n = 27 [a]	96 (77–131)
FEV_1% predicted at Visit 1, median (range)	86 (64–122)
Change in FEV % predicted from baseline to visit 1, median (range) n = 27	−10 (−45, 4)
Visit 1 PES total score, median (range) n = 27 [b]	6 (5–16)
CF respiratory culture results at visit 1	
No CF pathogens detected	4 (14%)
Methicillin sensitive Staphylococcus aureus	13 (46%)
Methicillin Resistant Staphylococcus aureus	5 (18%)
Pseudomonas aeruginosa	8 (29%)
Stenotrophomonas maltophilia	5 (18%)
Aspergillus	3 (11%)
Haemophilus influenzae	2 (7%)
Achromobacter xylosoxidans	1 (4%)
Other	3 (11%)
Positive Viral PCR at visit 1	11 (39%)
Antibiotic class prescribed	
Sulfa	12 (43%)
Penicillin	9 (32%)
Fluroquinolone	5 (18%)
Cephalosporin	1 (3.5%)
Oxazolidinone	1 (3.5%)
Days between visits, median (range)	18 (14–21)

[a] One subject did not have an FEV1 recorded in the prior six months.
[b] One subject did not have a documented PES.

3.3. Pulmonary function changes

Subjects enrolled in the study had a median baseline FEV_1 of 95% predicted (Range: 77, 131%). At the first visit, a median decrease of 10% (Range: −45%, 4%) in FEV_1% predicted was observed with a median FEV_1 value of 86% predicted (Range: 64, 122%). Following oral antibiotic treatment, there was a median increase in FEV_1 of 9% predicted (Range: −8%, 31%; $p < 0.01$) (Fig. 1). After two weeks of antibiotics, 22 (81%) subjects returned to ≥90% of baseline, 17 subjects (63%) returned to ≥95% of their baseline and 15 subjects (56%) returned to ≥100% from their previous baseline. For those 5 subjects that did not return to within 90% of their baseline further treatment was guided by their primary CF provider; 3 received an additional two weeks of oral antibiotics, 1 was hospitalized and 1 received no further treatment. Additional antibiotic courses were not started until completion of visit 2 measurements. There was no correlation between the change in the respiratory domain of the CFR-Q and recovery to baseline FEV_1 ($r = 0.16$, $p = 0.49$). There was also no correlation between recovery to baseline FEV_1 and total number of airway clearance treatments performed ($r = 0.01$ and $p = 0.97$).There was no difference in the change in FEV_1 based on the length of time between visits 1 and 2 (see Supplemental Fig. 4). Among the 27 subjects who underwent pre- and post-bronchodilator pulmonary function testing

Table 2
Changes in clinical and laboratory outcomes with oral antibiotic treatment.

	Median change (range)	p-Value
Changes in pulmonary function		
Change in FEV1 absolute (L)	0.22 (−0.27, 0.89)	< 0.01
Change in FEV1% predicted	9 (−8, 31)	< 0.01
Symptom changes		
Change in PES total scores, median (range), n = 27	−6 (−16, 2)	< 0.01
Patient reported change in CFQ-R respiratory domain, n = 23	16.7 (−5.6, 66.7)	< 0.01
Parent reported change in CFQ-R respiratory domain, n = 12	22.2 (0, 72.2)	< 0.01
Microbiology changes		
Change in $\log_{10}$CFU of dominant bacteria, median (range), n = 17	−0.82 (−8, 2)	0.03
Changes in sputum inflammatory markers		
Elastase (μg/mL)	−37 (−464, 272)	0.02
IL-1β (pg/mL)	-2.8×10^3 (-69.3×10^3, 33.0×10^3)	0.03
IL-8 (pg/mL)	1.4×10^4 (-16.5×10^4, 35.6×10^4)	0.12
HMGB-1 (ng/mL)	5.4 (−824, 199)	0.59
White blood cell count, n = 9	-0.2×10^3 (-3.3×10^3, 1.4×10^3)	0.20
Percent neutrophils, n = 9	0 (−15, 48)	0.66

performed at visit 1, 8 (29%) had airway hyperreactivity as defined by an increase in FEV_1 of ≥12% and/or an increase in Forced Expiratory Flow at 25–75% (FEF_{25-75}) ≥ 32%. Significant improvements post-bronchodilator were not associated with FEV_1 improvement following antibiotic treatment. Two of these patients with airway hyperreactivity received a 5 day course of oral steroids concomitant with their antibiotics. Post-antibiotics, five subjects had airway hyperreactivity (3 subjects had hyperreactivity at both visits, 2 had hyperreactivity at visit 2 but not at visit 1). One subject who did had hyperreactivity at visit 1 did not have post-bronchodilator testing completed at visit 2.

Pulmonary function testing was also captured at routine clinic visits for 6 months after the exacerbation. There was a median decrease of −2% (−23%, 24%) in highest FEV_1% predicted over the subsequent 6 months compared to the FEV_1% predicted at the end of the exacerbation.

3.4. Viral infection and microbiology changes

Viruses were detected in 11/28 subjects (39%) with rhinovirus/enterovirus being detected most commonly (n = 8) followed by coronavirus (n = 2) and RSV (n = 2). One subject had two viruses detected (RSV and coronavirus). There was no relationship between viral positivity and season (Supplemental Fig. 5). There was no correlation between the presence of a positive viral PCR and decrease in FEV_1 from baseline at the time of an exacerbation. The change in lung function with oral antibiotics was not significantly different between those infected with a virus and those without viral infection (p = 0.19).

CF respiratory culture results obtained at the first study visit are listed in Table 1. Methicillin sensitive and methicillin resistant *Staphylococcus aureus* (*MSSA* and *MRSA*) and *P. aeruginosa* were the most frequently detected CF pathogens in the initial sputum cultures. Paired sputum samples collected at visits 1 and 2 with detected pathogens at visit 1 were obtained in 17 of 28 subjects (n = 4 negative at visit 1, n = 2 insufficient quantity at visit 1, n = 5 insufficient quantity at visit 2). Of these 17 matched samples, 15 expectorated at both visits and 2 expectorated at the initial visit but required a sputum

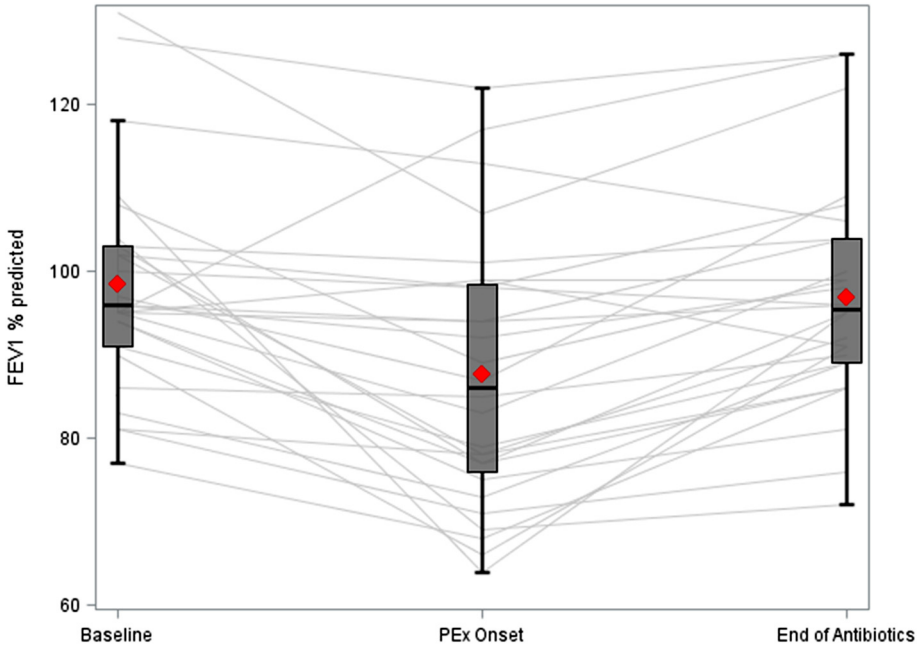

Fig. 1. Change in FEV1% predicted and time of PEx with oral antibiotic treatment: FEV1 percent predicted was captured at baseline (highest FEV_1 value in prior 6 months), PEx and end of antibiotic treatment. At PEx onset there was a median decrease in FEV_1% predicted of 10% (p < 0.01). Following a two week course of oral antibiotics there was a median increase in FEV_1% predicted of 9% (p < 0.01).

induction at follow up. Sputum samples were insufficient in 8 samples (2 at visit 1, 6 at visit 2) out of a total of 56 samples (failure to collect sputum rate: 14%, 95% CI: 6%–26%). The median bacterial density of the dominant organism at the start of an exacerbation was 5.0 $\log_{10}$ (range 3.0, 9.6) colony forming units (cfu/mL). Among these 17 subjects, 13 (76%) had a decrease in bacterial colony count of the dominant organism. Following antibiotic treatment, there was a median (range) decrease of 0.8 $\log_{10}$ cfu/mL (−8 $\log_{10}$, 2 $\log_{10}$, p = 0.03) in these 17 subjects (Fig. 2). There was a median increase in *MSSA* of 1.7 $\log_{10}$ cfu/mL, while bacterial density of *MRSA* and *P. aeruginosa* both decreased 3.3 $\log_{10}$ cfu/mL. The most common antibiotic prescribed in subjects with MSSA as the primary bacterium on sputum culture was amoxicillin-clavulanic acid (n = 8). Of the 8 patients who grew MSSA on their sputum cultures and were treated with amoxicillin-clavulanic acid, 7 had improvement in FEV_1 to 100% or greater of their prior baseline. The remaining subject was at 94% of prior baseline. Therefore, the lack of reduction in bacterial density was not congruent with clinical improvement observed in this subset of patients. Neither baseline bacterial density nor change in bacterial density were associated with recovery of baseline FEV_1 in the entire cohort. There was no difference in the change of bacterial density based on the length of time between visits 1 and 2 (see Supplemental Fig. 4).

3.5. Changes in sputum inflammation

There was a significant decrease in sputum NE activity [median (range) -37 μg/mL (−464, 272), p = 0.02] and IL-1β [-2.8×10^3μg/mL (-6.9×10^4, 3.3×10^4), p = 0.03] (Fig. 3). No significant changes were observed in sputum IL-8 (p = 0.12) or HMGB-1 (p = 0.59). Among the 9 patients with paired cytology assessments, there were no significant differences in total white blood cell count (p = 0.2) and percent neutrophils (p = 0.66). There was no association between baseline NE, IL-1β, change in NE or change in 1 L-1β and return to baseline FEV_1. There were also no correlations between changes in sputum inflammatory markers and changes in bacterial density.

3.6. Risk factors for failing to return to baseline lung function

FEV_1% predicted at the start of a PEx and age were associated with recovery to baseline FEV_1. The r-square for the final model was 0.68 and both variables were positively associated with increased likelihood of recovery to baseline FEV_1, meaning that those who were older and had a higher FEV_1% predicted at the start of an exacerbation were more likely to recover to within 90% of their prior baseline.

4. Discussion

PEx are common in CF and are frequently treated with oral antibiotics in the outpatient setting despite limited evidence demonstrating their effectiveness. There are several notable findings from this prospective study of oral antibiotic treatment of PEx in school aged children with CF. Patients in this study reported feeling better following a two week course of oral antibiotics with significant improvements seen in PES and the CFQ-R respiratory domain. Lung function significantly improved though, of note, approximately 20% of subjects failed to return to within 90% of their baseline FEV_1 value at the

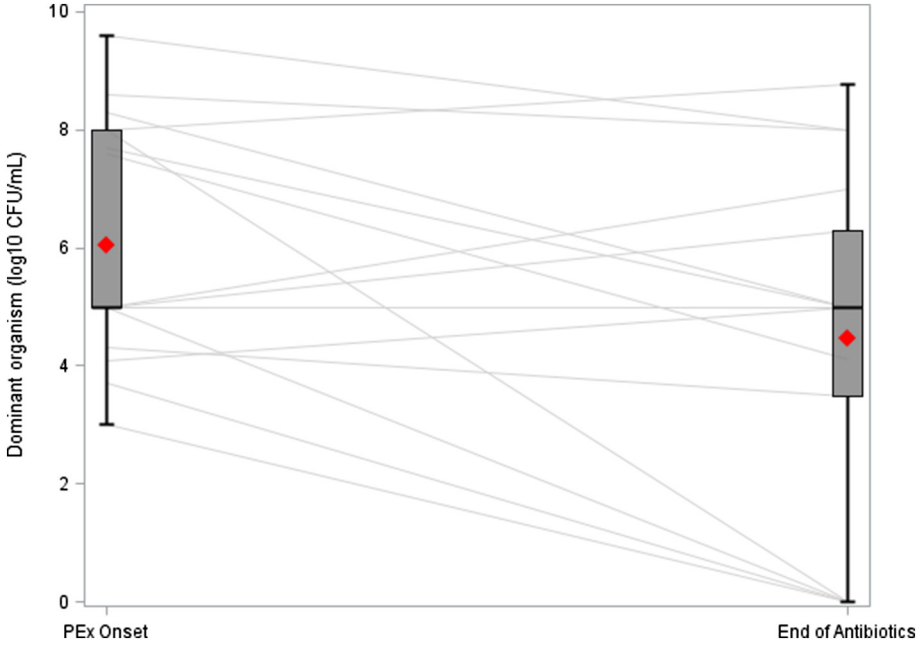

Fig. 2. Changes in sputum bacterial density of dominant bacteria with oral antibiotic treatment: Bacterial density of the primary bacterial pathogen detected on sputum culture was measured at PEx onset and at the end of antibiotics in a subset of patients (n = 17). A median decrease of 0.8 $\log_{10}$ cfu/mL (−8 $\log_{10}$, 2 $\log_{10}$, p = 0.03) was observed.

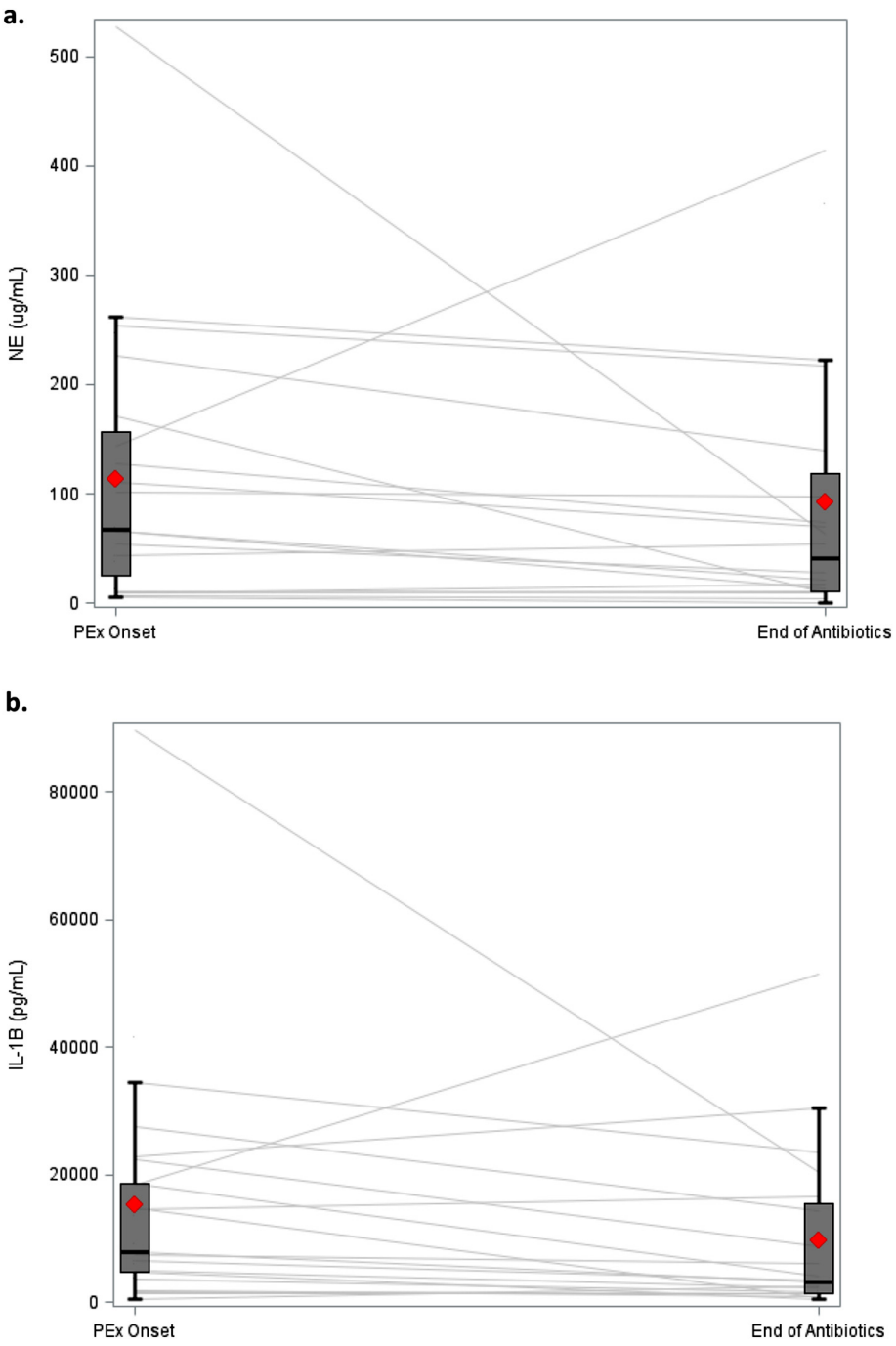

Fig. 3. Changes in sputum inflammatory markers with oral antibiotic treatment: Sputum inflammatory markers were measured at PEx onset and at the end of antibiotic treatment. There was a significant decrease in a) sputum NE activity [median (range) -37 μg/mL (−464, 272), p = 0.02] and b) IL-1β [-2.8×10^3μg/mL (-6.9×10^4, 3.3×10^4), p = 0.03]. No significant changes were observed in sputum IL-8 (p = 0.12) or HMGB-1 (p = 0.59) (not pictured).

completion of two weeks of antibiotic therapy. Additionally, antibiotic treatment was associated with significant decreases in sputum bacterial density, sputum NE and IL-1β.

Much of our knowledge of CF PEx treated in the outpatient setting is derived from retrospective studies. Registry-based studies have found that more frequent prescribing of antibiotics is associated with better lung function [13], though exacerbations treated with oral antibiotics are associated with less improvement in FEV_1 [2] and a decreased likelihood of returning to baseline lung function [14] compared to IV treatment. A single center retrospective study highlighted that approximately 25% of subjects failed exacerbation treatment with oral antibiotics and required treatment with IV antibiotics [3]. Additionally, Stanojevic and colleagues evaluated drop in FEV_1 at the start of an exacerbation and improvements in FEV_1 at the end of oral antibiotic treatment and long term follow up (within three months) in a large cohort of patients with CF [4]. Although a lower proportion of their subjects had FEV_1

determinations at the end of treatment, approximately two-thirds recovered to within 90% of baseline at the completion of oral antibiotic treatment. This further improved to just over 80% at subsequent follow up (best values within three months). They also demonstrated that decline in FEV_1 was greater in those with more frequent exacerbations. The population studied by Stanojevic and colleagues was older and had more significant underlying lung disease based on average FEV_1 compared to our cohort. Additionally, given the retrospective nature of the study, only a subset had a follow-up evaluation at the time of antibiotic completion (264 out of 626). It is also unclear if this smaller subset may have reflected a group that remained symptomatic and thus were more likely to receive close follow-up rather than reflecting overall population, which may explain why the return to baseline lung function is lower at this time point.

Ratjen and colleagues performed a similarly designed prospective study and examined changes in clinical outcomes, bacterial density, and airway inflammation following oral antibiotic treatment for a PEx in 17 pediatric patients with CF [15]. While they reported improvements in exacerbation symptom scores, FEV_1, and reductions in bacterial density, similar to our cohort, they did not observe significant changes in sputum inflammatory markers, including NE activity, in contrast to our cohort. This is surprising given that their patients had a lower baseline FEV_1, higher sputum bacterial density, and higher sputum IL-8 compared with our cohort, and were treated with 3 weeks, rather than 2, of antibiotics. Further studies with larger numbers of subjects are needed to more definitively determine the effects of oral antibiotics on measures of airway inflammation.

Treatment of exacerbations in the inpatient setting with IV antibiotics has been more extensively studied. These studies have demonstrated that a significant number of subjects fail to return to within 90% of their baseline lung function [5, 6, 16] and interestingly, is comparable to the percentage of subjects that did not return to baseline lung function in our cohort. This inpatient treatment benefit may be due in part to a more intensive airway clearance regimen. The reduction in sputum bacterial density in our cohort is lower than what has been reported in those being treated with IV antibiotics for a PEx [7]. The lesser reduction in bacterial density in our subjects may be due to increased efficacy of IV antibiotics treating bacteria from the lower airways, different antibiotic options available in IV form or different spectrum of activity for IV antibiotics compared to oral treatment. Another possibility is that more intensive airway clearance regimens during a hospitalization further facilitate clearing of bacteria from the lower airways. In our cohort, there was no association between the number of airway clearance treatments performed and recovery of baseline FEV1. It is important to note that change in bacterial density may not predict clinical response as observed in our study and a study of patients receiving IV antibiotics targeting *P. aeruginosa* [17]. One study also found that viral infection did not alter the bacterial density in patients with *P. aeruginosa* being treated for a CF PEx [18]. However, in another study of CF exacerbations treated with IV antibiotics, detection of viruses was associated with less treatment response [19] in contrast to our findings where viral infection did not appear to influence treatment response. It is possible that this is reflective of the severity of the viral illness or exacerbation accounting for the differences in inpatient versus outpatient outcomes or that we did not have a sufficient number of subjects to identify a similar trend. Treatment with IV antibiotics has also been associated with reduction in airway inflammation, specifically sputum NE measurements [7, 20] as seen in our cohort although the decrease in NE was greater with IV antibiotic treatment (0.4 $\log_{10}$) [7] compared to a 0.2 $\log_{10}$ reduction with oral antibiotic treatment in our cohort.

Symptomatic improvement is a key outcome of PEx treatment for patients with CF. Interestingly, improvement in PES and CFQ-R did not correlate with FEV_1 improvement in our cohort. Similarly, there was no significant correlation between symptomatic improvement and lung function recovery in a study of PEx treated with IV antibiotics [21]. This suggests that patient report alone is insufficient for defining resolution of an exacerbation if the definition of resolution also includes FEV_1 recovery. Furthermore, a larger improvement in FEV_1 was observed when the goal for discharge during an exacerbation treated with IV antibiotics was based on improvement in lung function rather than symptomatic improvement [22].

Limitations of our study include enrollment of a relatively small number of subjects at a single center. This was offset in part by our prospective design and comprehensive collection of clinical and laboratory data. While there was concern regarding a selection bias, enrolling patients who lived closer to our CF Center and were able to return for follow up in 2–3 weeks, the characteristics of our cohort generally reflect those of our overall clinic population. A seasonality bias is less likely as enrollment occurred over more than a 12 month period. There may be a bias in the airway clearance treatment frequency due to self-reporting. Additionally, our patient cohort had milder lung disease (preserved lung function, not all routinely expectorated sputum); thus, our findings may not be generalizable to those with more moderate and severe lung disease. Viral testing was performed on expectorated sputum instead of nasal washings which may have limited our detection of viruses. However, the high detection rate of viruses (over one third of samples) suggests that viruses are frequently present at the time of PEx treatment in school age children with CF. Additionally, viral testing was only performed at visit 1. It is plausible that subjects may have acquired a new virus during the 2–3 weeks between visits which may have impacted the measurements performed in the study. In a larger cohort, stratifying based on type of virus could be clinically meaningful but could not be performed in this study due to the small number of subjects (n = 11) who tested positive for a virus. It is also possible that the study was underpowered for sputum bacterial density and inflammatory markers. The study was powered based on 30 subjects; however, only 17 subjects had matched samples to evaluate the primary outcome of reduction in bacterial density. This may have affected our ability to detect significant changes in sputum inflammatory markers given the

variability of these measures. Finally, the study is limited by the absence of a control group and therefore it is unclear if the improvements seen in the majority of subjects were related to treatment with oral antibiotics, airway clearance or a combination of both.

This study raises important questions related to the management of PEx. Maintenance of lung function remains a priority in the care of pediatric patients with CF. There is a need to more conclusively identify the risk factors associated with failure to recover to baseline lung function. As symptomatic improvement did not correlate with lung function recovery, closer monitoring of lung function should be considered to optimize PEx treatment in the outpatient setting. This may include standardized protocols for the diagnosis and treatment of PEx, home monitoring during an exacerbation, spirometry only visits, and scheduling sooner CF clinic visits following an exacerbation. Additionally, a better understanding of how lung function is affected longitudinally is needed especially given the important findings that more frequent PEx are associated with a greater rate of FEV_1 decline [4]. Longitudinal assessment is also necessary as short-term clinical improvement may not be associated with long term outcomes including time to next exacerbation [21]. Treatment of PEx on an outpatient basis with oral antibiotics are likely to increase as more patients with CF are being treated with CFTR modulators which have been found to result in fewer hospitalizations and exacerbations [23, 24].

In this cohort of school-aged children with CF, we found that treatment with a two-week course of oral antibiotics was associated with significant improvements in patient reported outcomes, lung function, bacterial density and sputum inflammatory markers. However, this study also identified that approximately 20% of subjects failed to return to within 90% of their baseline lung function. There remains a gap in our understanding of PEx treatment, as many patients fail to recover baseline lung function despite symptomatic improvement. Future studies are needed to optimize treatment of PEx in the outpatient setting with oral antibiotics, with our data serving as a point of reference for expected clinical and laboratory response.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2018.05.015.

Conflict of interest statement

The authors report grant funding from the Cystic Fibrosis Foundation (Hoppe, Sagel) and National Institutes of Health (Zemanick, Sagel) as potential conflicts of interest.

Author contributions

Conception and design of the study: J.E.H, B.D.W, F.J.A, E.T.Z and S.D.S; Data acquisition: J.E.H, E.T.Z and S.D.S; Analysis and Interpretation of Data: J.E.H, B.D.W, F.J.A, E.T.Z and S.D.S; J.E.H drafted the initial manuscript and B.D.W, F.J.A, E.T.Z and S.D.S critically reviewed it for intellectual content. All authors approve of this final version.

Sources of support

This work was supported by the Cystic Fibrosis Foundation (HOPPE14D0, HOPPE16A0) and the National Institutes of Health: NHLBI/NIH (K23 HL114883-01A1, Zemanick) and NIH/NCATS (Colorado CTSI Grant Number UL1 TR001082) - Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

Acknowledgements

The authors wish to thank the CF Research Coordinators at Children's Hospital Colorado for their invaluable help in the recruitment of patients and coordination of research visits, the laboratory technicians in the Pediatric Clinical Translational Research Center Core Laboratory at Children's Hospital Colorado for their outstanding technical assistance in this work, and Dr. Marci Sontag for her critical review of this manuscript. This work was supported by the Cystic Fibrosis Foundation (HOPPE14D0, HOPPE16A0) and the National Institutes of Health: NHLBI/NIH (K23 HL114883-01A1, Zemanick) and NIH/NCATS (Colorado CTSI Grant Number UL1 TR001082) - Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

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