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Evaluating FEV1 decline in diagnosis and management of pulmonary exacerbations in children with cystic fibrosis

Drake C. Bouzek MD[1] | Clement L. Ren MD[2] | Misty Thompson BS[1] | James E. Slaven MS[3] | Don B. Sanders MD[1]

[1]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[3]Department of Biostatistics & Health Data Science, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence

Drake C. Bouzek, MD, Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children, 705 Riley Hospital Dr, ROC 4270, Indianapolis, IN 46202, USA.
Email: dbouzek@iu.edu

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Abstract

Rationale: Forced expiratory volume in 1 s (FEV1) decline (ΔFEV1) is associated with pulmonary exacerbation (PEx) diagnosis in cystic fibrosis (CF). Spirometry may not be available during telehealth visits and could impair clinician ability to diagnose PEx. This study aims to (1) identify the associations between degrees of ΔFEV1 (decrease of <5% predicted vs. 5%–9% predicted vs. ≥10% predicted from baseline), clinical symptoms, and clinician-diagnosed PEx and (2) evaluate the correlation between respiratory symptoms, ΔFEV1, and antibiotic treatment.

Methods: Retrospective, descriptive study of PEx diagnosis and management in 628 outpatient clinical encounters with spirometry in 178 patients with CF ages 6–17 years at Riley Hospital for Children during 2019. Odds ratios (OR) of symptoms associated with clinician-defined PEx diagnosis and antibiotic management stratified by ΔFEV1 decline were determined.

Results: Clinician-diagnosed PEx occurred at 199 (31.7%) visits; increased cough (77.4%) and sputum/wet cough (57.8%) were the most frequently reported symptoms. Compared to no ΔFEV1, the odds of a clinician-diagnosed PEx were increased when $\Delta FEV1_{5\%-9\%}$ and $\Delta FEV1_{\geq 10\%}$ was present with increased cough (OR 1.56, 95% confidence interval [CI] 1.25–1.94 and OR 1.82, 95% CI 1.52–2.19, respectively), increased sputum (OR 1.59, 95% CI 1.20–2.12 and OR 1.78, 95% CI 1.37–2.32, respectively), and increased cough and sputum together (OR 1.51, 95% CI 1.08–2.13 and OR 1.68, 95% CI 1.22–2.31, respectively).

Conclusions: ΔFEV1 is associated with increased likelihood that cough and sputum are diagnosed as a PEx. Spirometry is essential for PEx diagnosis and treatment and is a necessary component of all clinical encounters.

KEYWORDS

antibiotic therapy, cystic fibrosis, pulmonary exacerbations, pulmonary function testing

1 | INTRODUCTION

Cystic fibrosis (CF) lung disease is characterized by recurrent pulmonary exacerbations (PEx), which are associated with progressive loss of lung function,[1,2] diminished quality of life,[3,4] and increased mortality.[5] PEx are frequently treated with antibiotics, and although a goal of treatment is to recover to prior baseline levels, some patients experience irreversible loss of pulmonary function.[6–10] Diagnostic criteria for PEx are poorly defined and vary by institution, and even within institutions.[11–16] Different combinations of symptoms, lung examination findings, spirometry, and clinician decision to treat with antibiotics (intravenous, inhaled, or oral) have been used in clinical trial definitions of PEx.[17–23] Cough, increased sputum production, and dyspnea are the clinical symptoms most frequently used to diagnose PEx.[17,18,20,24] Decline in forced expiratory volume in 1 s (FEV1) is associated with PEx diagnosis,[25–27] but changes in FEV1 are often only weakly correlated with clinical symptoms.[17,28]

Most PEx are diagnosed in the outpatient setting and treated with oral antibiotics.[9,25,29,30] Telehealth became more prevalent during the COVID-19 pandemic and is likely to be used in CF care in the future.[31,32] A consequence of this shift is that many PEx treatment decisions will be made without the ability to evaluate objective markers of PEx such as crackles on lung exam or decline in FEV1. It is important to identify how pulmonary function testing is utilized in relation to clinical symptoms to diagnose PEx to understand how the inability to measure pulmonary function will affect PEx treatment decisions. The aims of this study are to (1) identify the concordance between degrees of FEV1 decline (decrease of <5% predicted vs. 5%–9% predicted vs. ≥10% predicted from baseline), clinical symptoms, and clinician-diagnosed PEx and (2) evaluate the correlation between respiratory symptoms and PEx diagnosis and management according to FEV1 decline. We hypothesize that in the presence of respiratory symptoms, greater declines in FEV1 are associated with a greater likelihood of PEx diagnosis and treatment with antibiotics.

2 | METHODS

2.1 | Study population and design

We performed a retrospective chart review of children with CF followed at the Riley Hospital for Children CF Center (Indianapolis, IN) to evaluate the roles of symptoms and ΔFEV1 in PEx diagnosis and management. Children ages 6–17 years old in 2019 with a diagnosis of CF determined by the presence of two known CF-causing CF therapies (CFTR) mutations and/or sweat chloride ≥60 mEq/L were eligible for inclusion. Data were collected from all outpatient clinic encounters in the calendar year 2019 at Riley Hospital for Children that included spirometry results that meet standardized criteria for acceptability. The presence of a PEx was based on the treating clinician's diagnosis. Because resolution of PEx is often not documented, encounters within 4 weeks of a documented PEx were excluded from our analysis.

Demographic variables including age on December 31, 2019, sex, race, CFTR genotype, respiratory microbiologic culture results for 12 months before each clinical encounter, use of CF therapies (CFTR modulator, pancreatic enzymes, dornase alfa, chronic inhaled tobramycin, azithromycin, and hypertonic saline), and insurance status (Medicaid, private) were obtained from the electronic medical record. Microbiologic culture data is presented as "present" or "absent" in a patient considering all sputum samples collected in 2019, with some patients harboring multiple species. Clinical symptoms, body mass index (BMI) percentile, lung auscultation findings, baseline and encounter FEV1 percent predicted, and decline in FEV1 percent predicted from baseline (ΔFEV1) were obtained for each encounter from the electronic medical record. Percent predicted FEV1 was calculated using Global Lung Initiative (GLI) reference equations.[33] Median FEV1 and BMI percentile for the study cohort were calculated from the FEV1 and BMI percentiles at the first reported clinical encounter on or after January 1, 2019.

For each included encounter, baseline FEV1 percent predicted was defined as the average of the two highest FEV1 values in the 12 months before the encounter. FEV1 decline (ΔFEV1) was determined by the decrease from baseline FEV1 percent predicted and categorized as no change or improved from baseline, <5% decline ($\Delta FEV1_{<5\%}$), 5%–9% decline ($\Delta FEV1_{5\%-9\%}$), or ≥10% decline ($\Delta FEV1_{\geq 10\%}$) from baseline. Whether the treating clinician diagnosed a PEx and whether a course of antibiotics (Oral or Intravenous) was prescribed were recorded. PEx was defined as a clinical encounter with provider documentation of PEx in the encounter note or if PEx was included in the International Classification of Diseases, Tenth Revision (ICD-10) coding for the encounter. Standardized PEx diagnostic criteria do not currently exist at Riley Hospital for Children. Chronic oral and inhaled antibiotics, or antibiotics used for *Pseudomonas* eradication, were not included as PEx treatments. The Indiana University Institutional Review Board approved this study. HIPAA standards were maintained and consent was waived during the study.

2.2 | Statistical analysis

Descriptive statistics were used to characterize patients included in the study. χ^2 tests were performed to determine if there was significant heterogeneity between PEx groups with nonordered variables, with Mantel–Haenszel χ^2 tests being used to evaluate differences for ordered categorical data. Generalized Estimating Equations (GEEs) were performed, using logistic regression analysis, to determine the odds of PEx diagnosis or antibiotic prescription for encounters with increased cough, increased sputum, or increased cough and sputum, based on ΔFEV1 (any decline, compared to remaining stable) compared to encounters with the same symptoms. Increased cough, increased sputum, and increased cough and sputum were selected for the model because they were the most frequently

reported symptoms in PEx and most reliably documented in the EMR. GEEs were also performed to determine the odds of PEx diagnosis for encounters with weight loss, abnormal lung examination, or increased cough and the presence of at least one subjective symptom (fatigue, decreased appetite, fever, missed school, dyspnea, wheezing, or hemoptysis). These GEEs allow for the use of covariates in a multivariate model, adjusting for baseline FEV1 values, and to accurately account for repeated measures, as each participant could have more than one PEx encounter. All analytic assumptions were verified. Analyses were performed using SAS v9.4 (SAS Institute).

3 | RESULTS

3.1 | Cohort characteristics

In 2019, there were 628 outpatient clinical encounters among 178 children with CF 6–17 years of age at Riley Hospital for Children. Patient demographic and clinical characteristics are shown in Table 1. Among the 628 outpatient clinical encounters, a clinician-diagnosed PEx was present for 199 (31.7%) visits. As expected, clinician-reported symptoms, abnormal breath sounds on auscultation, and weight loss were more common in PEx encounters (Table 2). Symptom duration was longer in PEx encounters ($p < 0.001$, Table 2). Symptom duration greater than or equal to 3 days occurred more frequently in encounters with PEx diagnosis compared to encounters with no PEx diagnosis (77.8% vs. 35.5%, Table 2). The mean standared deviation difference in FEV1 percent predicted from baseline for PEx encounters was −13.1 ± 9.0, and −2.4 ± 9.0 for encounters without a PEx. $\Delta FEV1_{<5\%}$ (12.1% vs. 36.4%) and no change in FEV_1 (4.5% vs. 34.0%) were more frequently observed in encounters without a PEx compared to encounters with a PEx ($p < 0.0001$, Table 2).

3.2 | FEV1 decline and PEx diagnosis

The proportion of encounters with increased cough or increased sputum that were diagnosed as a PEx was higher in the presence of ΔFEV1 (Table 3). For example, only 26.9% of encounters with cough and no change in FEV1 were diagnosed as a PEx; this proportion increased to 47.9%, 71.1%, and 86.8% for $\Delta FEV1_{<5\%}$, $\Delta FEV1_{5\%–9\%}$, and $\Delta FEV1_{\geq 10\%}$, respectively. Forty-seven encounters demonstrated $\Delta FEV1_{\geq 10\%}$ and no PEx diagnosis (Table 2). Compared to encounters with $\Delta FEV1_{\geq 10\%}$ and no PEx diagnosis, encounters with $\Delta FEV1_{\geq 10\%}$ and PEx diagnosis had lower baseline FEV1 (101.7 ± 13.0% vs. 94.4 ± 16.3%, $p < 0.01$) and more frequent reports of increased cough (77% vs. 30%), increased sputum (60% vs. 16%), fatigue (26% vs. 3%), dyspnea (14% vs. 0%), wheezing (12% vs. 0%), weight loss (39% vs. 21%), and abnormal lung examination findings (36% vs. 2%) (Supporting Information: Table E1). In multivariate regression models that adjusted for within-person correlation and baseline FEV1, $\Delta FEV1_{5\%–9\%}$, and $\Delta FEV1_{\geq 10\%}$ were associated with increased odds of PEx diagnosis in the presence of increased cough, increased sputum, and increased cough and increased sputum together (Figure 1). The presence of $\Delta FEV1_{<5\%}$ with increased cough, increased sputum or wet cough, and increased cough and sputum together trended toward an increased likelihood of PEx diagnosis but did not reach statistical significance (Figure 1). The presence of increased cough with at least one additional subjective symptom

TABLE 1 Study population characteristics

Total patients, *n*	178
Number of females, *n* (%)	84 (47.2)
Nonwhite or Hispanic, *n* (%)	18 (10.1)
Age in years, median (IQR)	11.5 (8–14)
Genotype, *n* (%)	
F508del/F508del	97 (54.5)
F508 heterozygous	61 (34.3)
Other/unknown	20 (11.2)
CFTR modulator, *n* (%)	
Tezacaftor–ivacaftor	23 (12.9)
Ivacaftor	21 (11.8)
Lumacaftor–ivacaftor	52 (29.2)
Elexacaftor–tezacaftor–ivacaftor	2 (1.1)
None	80 (44.9)
Other chronic CF therapies, *n* (%)	
Pancreatic enzymes	165 (92.7)
Dornase alfa	151 (84.8)
Inhaled tobramycin	54 (30.3)
Azithromycin	43 (24.3)
Hypertonic saline	131 (74.4)
Baseline BMI percentile, median (IQR)	55.9 (31.4–76.3)
Baseline FEV1% predicted, median (IQR)	96 (84–104)
Respiratory culture, *n* (%)	
Methicillin-sensitive Staphylococcus aureus	134 (75.3)
Methicillin-resistant Staphylococcus aureus	60 (33.7)
Pseudomonas	63 (35.4)
Insurance, *n* (%)	
Medicaid	90 (47.8)
Private	85 (47.8)
Other	2 (1.1)
None	1 (0.6)

Abbreviations: BMI, body mass index; CFTR, cystic fibrosis therapies; FEV, forced expiratory volume; IQR, interquartile range; MRSA, Methicillin-resistant Staphylococcus aureus; MSSA, Methicillin-sensitive Staphylococcus aureus.

TABLE 2 Clinical characteristics of encounters according to presence or absence of clinician-diagnosed pulmonary exacerbations (PEx)

	PEx, *N* = 199	No PEx, *N* = 429	*p* Value[a]
Clinical signs and symptoms, *n* (%)			
No symptoms recorded	20 (10.1)	253 (59.0)	<0.0001
Increased cough	154 (77.4)	71 (16.6)	<0.001
Increased sputum or wet cough	115 (57.8)	33 (7.7)	<0.0001
Fatigue	40 (20.1)	17 (4.0)	<0.0001
Decreased appetite	37 (18.6)	28 (6.5)	<0.0001
Fever	20 (10.1)	10 (2.3)	0.0001
Missed school	18 (9.0)	28 (6.5)	0.21
Dyspnea	20 (10.1)	6 (1.4)	<0.0001
Wheezing	14 (7.0)	4 (0.9)	<0.0001
Hemoptysis (any)	4 (2.0)	5 (1.2)	0.48
Weight loss, *n* (%)	71 (35.7)	80 (18.6)	<0.0001
Abnormal lung exam, *n* (%)	55 (27.6)	23 (5.4)	<0.0001
	PEx, *N* = 126	**No PEx, *N* = 93**	***p* Value[b]**
Symptom duration, *n* (%)[c]			
<3 days	28 (22.2)	60 (64.5)	<0.0001
3–6 days	40 (31.8)	15 (16.1)	
7–14 days	43 (34.1)	9 (9.7)	
>14 days	15 (11.9)	9 (9.7)	
	PEx, *N* = 199	**No PEx, *N* = 429**	***p* Value[b]**
Encounter FEV1, *n* (%)			
No change from baseline	9 (4.5)	146 (34.0%)	<0.0001
$\Delta FEV1_{<5\%}$	24 (12.1)[c]	156 (36.4)	
$\Delta FEV1_{5\%–9\%}$	46 (23.1)	80 (18.7)	
$\Delta FEV1_{\geq 10\%}$	120 (60.3)	47 (11.0)	

Note: Percentages for clinical signs and symptoms and encounter FEV1 decline (ΔFEV1) based on total encounters with a clinician-diagnosed PEx (*N* = 199) or without a clinician-diagnosed PEx (*N* = 429).

Abbreviation: FEV, forced expiratory volume.

[a]*p* value calculated with Mantel–Haenszel χ^2 analysis.

[b]*p* value calculated with χ^2 analysis.

[c]Percentages for symptom duration based on total encounters with a clinician-diagnosed PEx (*N* = 126) or without a clinician-diagnosed PEx (*N* = 93) with documentation of reported symptoms.

(fatigue, decreased appetite, fever, missed school, dyspnea, wheezing, or hemoptysis) was significantly associated with increased likelihood of PEx diagnosis in encounters with $\Delta FEV1_{5\%–9\%}$ and $\Delta FEV1_{\geq 10\%}$, but not $\Delta FEV1_{<5\%}$ (Supporting Information: Figure E1).

TABLE 3 Clinician-defined pulmonary exacerbations (PEx) diagnosed based on presence of clinical symptoms and degree of FEV1 decline (ΔFEV1)

FEV1 decline	PEx, *n* (%)	No PEx, *n* (%)
Increased cough, *N* = 225		
No change, *n* = 26	7 (26.9)	19 (73.1)
$\Delta FEV1_{<5\%}$, *n* = 48	23 (47.9)	25 (52.1)
$\Delta FEV1_{5\%–9\%}$, *n* = 45	32 (71.1)	13 (28.9)
$\Delta FEV1_{\geq 10\%}$, *n* = 106	92 (86.8)	14 (13.2)
Increased sputum or wet cough, *N* = 148		
No change, *n* = 15	5 (33.3)	10 (66.7)
$\Delta FEV1_{<5\%}$, *n* = 26	16 (61.5)	10 (38.5)
$\Delta FEV1_{5\%–9\%}$, *n* = 30	24 (80.0)	6 (20.0)
$\Delta FEV1_{\geq 10\%}$, *n* = 77	70 (90.9)	7 (9.1)
Increased cough and increased sputum or wet cough, *N* = 132		
No change, *n* = 10	4 (40.0)	6 (60.0)
$\Delta FEV1_{<5\%}$, *n* = 23	16 (69.6)	7 (30.4)
$\Delta FEV1_{5\%–9\%}$, *n* = 27	22 (81.5)	5 (18.5)
$\Delta FEV1_{\geq 10\%}$, *n* = 72	66 (91.7)	6 (8.3)
No symptoms recorded, *N* = 273		
No change, *n* = 95	1 (1.1)	94 (98.9)
$\Delta FEV1_{<5\%}$, *n* = 94	1 (1.1)	93 (98.9)
$\Delta FEV1_{5\%–9\%}$, *n* = 51	7 (13.7)	44 (86.3)
$\Delta FEV1_{\geq 10\%}$, *n* = 33	11 (33.3)	22 (66.7)

Note: Percentages calculated from total encounters (PEx and no PEx) for a given FEV1 decline (no change, <5%, 5%–9%, ≥10%).

Abbreviation: FEV, forced expiratory volume.

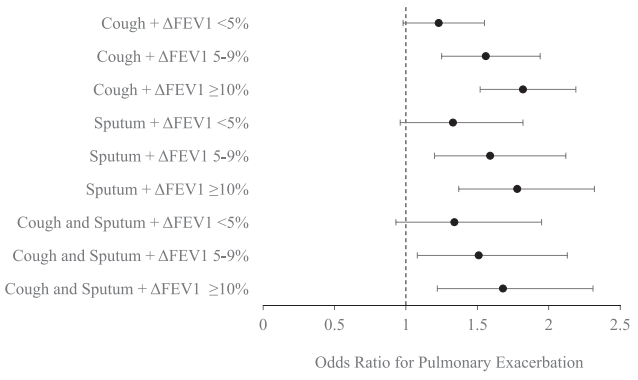

FIGURE 1 Odds ratios (OR) (black circles) with 95% confidence intervals (bars) of clinician-diagnosed pulmonary exacerbations based on combinations of symptoms and forced expiratory volume (FEV1) decline categories. OR adjusted for baseline FEV1 and within-person correlation with repeated measures analyses at encounter level.

TABLE 4 Antibiotic treatment for clinician-diagnosed pulmonary exacerbations (PEx) based on combinations of symptoms and FEV1 decline (ΔFEV1) categories

FEV1 decline	Antibiotics (%)	No antibiotics (%)
Increased cough, *N* = 164		
No change, *n* = 8	4 (50.0)	4 (50.0)
$\Delta FEV1_{<5\%}$, *n* = 26	23 (88.5)	3 (11.5)
$\Delta FEV1_{5\%-9\%}$, *n* = 34	26 (76.5)	8 (23.5)
$\Delta FEV1_{\geq 10\%}$, *n* = 96	85 (88.5)	11 (11.5)
Increased sputum or wet cough, *N* = 121		
No change, *n* = 6	3 (50.0)	3 (50.0)
$\Delta FEV1_{<5\%}$, *n* = 17	16 (94.1)	1 (5.9)
$\Delta FEV1_{5\%-9\%}$, *n* = 27	22 (81.5)	5 (18.5)
$\Delta FEV1_{\geq 10\%}$, *n* = 71	65 (91.5)	6 (8.5)
Increased cough and increased sputum or wet cough, *N* = 113		
No change, *n* = 5	3 (60.0)	2 (40.0)
$\Delta FEV1_{<5\%}$, *n* = 17	16 (94.1)	1 (5.9)
$\Delta FEV1_{5\%-9\%}$, *n* = 24	20 (83.3)	4 (16.7)
$\Delta FEV1_{\geq 10\%}$, *n* = 67	61 (91.0)	6 (9.0)
No symptoms recorded, *N* = 20		
No change, *n* = 1	1 (100.0)	0 (0.0)
$\Delta FEV1_{<5\%}$, *n* = 1	0 (0.0)	1 (100)
$\Delta FEV1_{5\%-9\%}$, *n* = 7	4 (57.1)	3 (42.9)
$\Delta FEV1_{\geq 10\%}$, *n* = 11	7 (63.6)	4 (36.4)

Note: Percentages calculated from total encounters (antibiotics and no antibiotics) for a given FEV1 decline (no change, <5%, 5%–9%, and ≥10%).
Abbreviation: FEV, forced expiratory volume.

The presence of abnormal lung examination findings or weight loss was significantly associated with increased likelihood of PEx diagnosis in encounters with $\Delta FEV1_{5\%-9\%}$ and $\Delta FEV1_{\geq 10\%}$, but not $\Delta FEV1_{<5\%}$ (Supporting Information: Figure E1).

3.3 | FEV1 decline and antibiotic use

Antibiotics (oral or IV) were more frequently prescribed in PEx encounters with increased cough or increased wet cough or sputum and any decline in FEV1 than if symptoms were present and there was no change in FEV1 (Table 4). Antibiotics (oral or IV) were more likely to be prescribed in the presence of increased cough and $\Delta FEV1_{<5\%}$ (OR 7.67, 95% CI 1.26–46.79, $p < 0.05$) and $\Delta FEV1_{\geq 10\%}$ (OR 7.73, 95% CI 1.75–34.07, $p < 0.05$). Antibiotic treatment (oral or IV) was also more likely in the presence of increased wet cough or sputum and $\Delta FEV1_{<5\%}$ (OR 16.00, 95% CI 1.22–210.59, $p < 0.05$) and $\Delta FEV1_{\geq 10\%}$ (OR 10.83, 95% CI 1.77–66.41, $p < 0.05$). No significant associations were identified when evaluating likelihood of antibiotic treatment in encounters with $\Delta FEV1_{5\%-9\%}$ and presence of increased cough (OR 3.25, 95% CI 0.65–16.21, $p = 0.151$) or increased wet cough or sputum (OR 4.40, 95% CI 0.68–28.55, $p = 0.120$). The presence of increased cough and increased sputum did not have a significant relationship with likelihood of antibiotic treatment for any ΔFEV1.

3.4 | FEV1 decline in the absence of symptoms

No symptoms were reported in 273 (43.4%) outpatient clinical encounters with $\Delta FEV1_{5\%-9\%}$ and $\Delta FEV1_{\geq 10\%}$ occurring in 51 (18.7%) and 33 (12.1%) of these encounters, respectively. A PEx was diagnosed in 20 (7.3%) encounters with no symptoms reported; almost all of these encounters (19/20) showed FEV1 decline (Table 3). The proportion of asymptomatic encounters diagnosed as a PEx increased with larger declines in FEV1 (Table 3). PEx encounters with increased cough or increased sputum and $\Delta FEV1_{5\%-9\%}$ and $\Delta FEV1_{\geq 10\%}$ were more frequently treated with antibiotics than PEx encounters with $\Delta FEV1_{5\%-9\%}$ and $\Delta FEV1_{\geq 10\%}$ and no reported symptoms (Table 4).

4 | DISCUSSION

Similar to previous studies in children with CF ages 6 years and older,[17,18] we observed that increased cough and increased sputum were the most frequently reported symptoms during PEx. We found that the presence of symptoms for 3 or more days was significantly more common in PEx and could be an important component of PEx diagnosis. We demonstrated that even small changes in FEV1 in the presence of increased cough or increased sputum are associated with the diagnosis of PEx and the use of antibiotics. Additionally, although only a minority of clinical encounters with no reported symptoms were diagnosed as a PEx, almost all (19/20) were associated with FEV1 decline. It is apparent that clinicians do not rely on FEV1 decline alone to make a PEx diagnosis. Forty-seven encounters with $\Delta FEV1_{\geq 10\%}$ did not yield a PEx diagnosis; these encounters typically had fewer reported signs and symptoms than encounters with $\Delta FEV1_{\geq 10\%}$ and a PEx diagnosis. In addition, encounters with $\Delta FEV1_{\geq 10\%}$ and no PEx diagnosis had higher baseline FEV1 than encounters with $\Delta FEV1_{\geq 10\%}$ and a PEx diagnosis, which is consistent with previous data showing that acute FEV1 decline is more likely to be diagnosed and treated as a PEx in individuals with lower baseline FEV1.[26] These findings highlight the extent to which clinicians use a combination of respiratory symptoms and FEV1 decline to diagnose PEx and prescribe antibiotics. Understanding this dynamic is key as the pandemic-era transition to telemedicine, in addition to the already frequent practice of prescribing antibiotics via telephone,[30] may further increase physicians' reliance on respiratory symptoms to diagnose PEx without spirometry.

The increasing prevalence of telemedicine requires clinicians to understand which signs and symptoms are predictive of PEx

diagnosis. Increased cough and increased sputum are well known to be linked to PEx diagnosis[17] and treatment with antibiotics,[18,20] but other symptoms also contribute to clinician decision to diagnose and treat PEx. In our study, subjective symptoms of fatigue, decreased appetite, fever, and dyspnea were observed more frequently in PEx encounters compared to encounters without PEx diagnosis. Although we excluded these symptoms from analysis due to inconsistent reporting in the EMR, which is a limitation of our study, these factors have been used in prior clinical decision-making tools. Previously validated PEx scoring tools use a combination of subjective symptoms such as fever, fatigue, school absenteeism, increased cough, change in sputum, dyspnea, and objective measurements (FEV1 decline, lung examination findings, and chest radiography) to create a standard approach for diagnosing and treating PEx.[16] Our study demonstrated that weight loss and abnormal lung examination findings significantly contribute to a physician making a PEx diagnosis in the presence of a decline in FEV1. Limitations in obtaining spirometry and chest radiography, performing lung auscultation, and obtaining reliable weight in virtual encounters render these current tools unfit for telemedicine visits and could lead to missed PEx diagnoses.

Our study highlights the importance of spirometry in clinician identification and treatment of PEx. Home spirometry provides clinicians data on lung function that may be useful for diagnosing PEx, but must be carefully interpreted given inconsistencies between home and in-clinic values. Numerous home spirometry products and applications have been developed for use in CF with varying cost and United States Food and Drug Administration approval.[34] Lechtzin et al. demonstrated that frequent symptom monitoring and use of home spirometry led to identification of more PEx but did not reduce the rate of lung function decline.[35] Home spirometry has also found to register significantly lower percent predicted FEV1 than clinic spirometry, which may cause some difficulties in interpretation.[36] Further studies will need to be performed to evaluate the ability of home spirometry devices to detect meaningful change in FEV1 and how these devices can be used with clinical symptoms to effectively diagnose PEx in telemedicine encounters.

In-person clinical encounters for people with CF were reduced during the pandemic and remained below 2019 levels even at the end of 2020.[37] PEx identified in clinic were greatly reduced, likely due to avoidance of viral respiratory infections or increased self-care during the pandemic.[37] However, it is possible that some of the reduction in PEx was due to the inability to measure changes in FEV1. The implication of not treating these "missed" PEx may not be clear for some time and will warrant future study.

We note that some PEx were not treated with antibiotics; most commonly patients were encouraged to increase adherence with airway clearance or chronic therapies, and/or to return to clinic for close follow up. This report highlights the importance of FEV1 decline in the diagnosis of PEx: clinicians are more likely to diagnose a PEx and treat with antibiotics when respiratory symptoms are present along with changes in FEV1. The ultimate risk of failing to treat PEx in children with CF is the potential for irreversible loss of lung function.[1,6,8] Many providers already diagnose PEx without spirometry and treat with antibiotics via telephone encounters.[30] The possibility of identifying PEx will become even more difficult in the future if telemedicine occurs more often given the absence of measurements of lung function, changes in weight, or chest examination. During the early stages of the pandemic, very few antibiotics were prescribed when telemedicine was prevalent.[37] It is not known if this was due to missed PEx, or the effects of social distancing and other lockdown measures. Ongoing research and clinical efforts to incorporate home spirometry may mitigate some of the difficulties of recognizing PEx. In addition, QI or research efforts to standardize the response to the presence of new respiratory symptoms noted on telehealth visits are needed to help overcome the absence of lung function data.

This study has several strengths. This is the first study to evaluate the degree of FEV1 decline while also considering the presence or absence of respiratory symptoms on likelihood of PEx diagnosis and antibiotic treatment.[17,18,20,24–26] Clinical symptoms and spirometry have been shown to increase the likelihood of PEx diagnosis and antibiotic usage independently.[17,18,25,29] Prior studies have evaluated FEV1 decline greater than 10% from baseline,[17,25] but this study is the first to evaluate small declines in FEV1 (<5%, 5%–9%) related to PEx diagnosis. Schechter et al. described significant improvement in their pediatric CF center's mean FEV1 with use of an algorithm that included more aggressive monitoring and treatment of small declines in FEV1.[27] Our study also includes patients on CFTR modulator therapy, which is important for understanding if and how PEx diagnosis and management changes in an era where the use of CFTR modulators is becoming more prevalent in pediatric patients. Flume et al. demonstrated that people with CF taking CFTR modulators who experience a PEx are still at-risk of failing to recover to prebaseline FEV1 levels.[38] Lastly, this study was performed at a large CF center allowing for a representative cohort to be assembled and increases the generalizability of the findings.

There are limitations to this study as well. Riley Hospital for Children does not have standardized criteria for diagnosing and treating PEx, which leads to variability in clinician diagnosis of a PEx as described by previous studies.[15,16,18] The PEx definition used in this study relies on appropriate documentation in the EMR and does not require specific criteria to be met. The retrospective nature of the study requires dependence on EMR documentation that places it at risk for missing data which hinders the ability to draw meaningful conclusions on the role of less-commonly reported symptoms or symptom duration. Additionally, EMR documentation may not reflect all criteria used by a clinician in diagnosing a specific individual PEx. Another limitation is that significant variance in the estimated OR of antibiotic use based on the presence of symptoms and FEV1 decline is present due to the low frequency of antibiotic usage in encounters with no FEV1 decline. The proportion of PEx treated with antibiotics was greater in encounters with increased cough or increased sputum and $\Delta FEV1_{<5\%}$ (88.5% and 94.1%, respectively) and $\Delta FEV1_{\geq 10\%}$ (88.5% and 91.5%, respectively) than in encounters with these

symptoms and $\Delta FEV1_{5\%-9\%}$ (76.5% and 81.5%, respectively). This could be due to sampling error and increasing the number of $\Delta FEV1_{5\%-9\%}$ encounters could make the proportions more similar to the $\Delta FEV1_{<5\%}$ and $\Delta FEV1_{\geq 10\%}$ encounters. Alternatively, these data could suggest that physicians are more likely to use nonantibiotic measures in PEx with intermediate FEV1 decline. Increasing the number of encounters could reduce the variance and provide a more precise estimate of the impact of FEV1 decline and the presence of symptoms on antibiotic usage, as well as adjusting for additional covariates in regression models. This study only included patients at a single center and the results could vary if other institutions were included. However, increased cough, increased sputum, and FEV1 decline have historically been frequently used by clinicians to diagnose PEx and treat with antibiotics.

Clinicians are more likely to diagnose a PEx and treat with antibiotics when respiratory symptoms are present along with changes in FEV1. Whether this practice is associated with optimal outcomes requires further study, although prior quality improvement programs support treatment of small declines in FEV1.[20] Diagnosing a PEx without spirometry and treating with antibiotics via telephone encounters is already a prevalent and frequent practice.[30] The utilization of telehealth could increase the number of encounters that require decision making without spirometry data while home spirometry methods continued to be developed and validated. This study highlights the need for increased awareness of the importance of FEV1 decline in PEx diagnosis. Spirometry should be included in each encounter when evaluating for PEx to ensure accurate diagnosis and treatment of all PEx. Until this is technologically feasible, a high index of suspicion for PEx is needed in telephone and telehealth encounters as spirometry data may not be available and PEx diagnoses could be missed.

AUTHOR CONTRIBUTIONS

Drake C. Bouzek: Conceptualization (equal); data curation (lead); formal analysis (supporting); methodology (equal); writing—original draft (lead); writing—review & editing (equal). **Clement L. Ren**: Conceptualization (equal); formal analysis (equal); methodology (equal); supervision (equal); writing—review & editing (equal). **James E. Slaven**: Formal analysis (lead); methodology (equal); writing—review & editing (equal). **Don B. Sanders**: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (equal); supervision (lead); writing—review & editing (equal).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Drake C. Bouzek http://orcid.org/0000-0002-8418-3072
Clement L. Ren http://orcid.org/0000-0003-4431-0644
Don B. Sanders http://orcid.org/0000-0001-6265-6249

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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