Procalcitonin predicts the severity of cystic fibrosis pulmonary exacerbations and readmissions in adult patients: a prospective cohort study

Kristina L Bailey ^{1,2}, Peter J Murphy,² Olena K Lineberry,² Matthew R Haack,² John D Dickinson,² Andre C Kalil³

¹Research Service, VA Nebraska-Western Iowa Health Care System, Omaha, Nebraska, USA

²Int Med-Pulmonary, University of Nebraska Medical Center, Omaha, Nebraska, USA

³Int Med-Infectious Disease, University of Nebraska Medical Center, Omaha, Nebraska, USA

Correspondence to

Dr Kristina L Bailey, Research Service, VA Nebraska-Western Iowa Health Care System, Omaha, NE 68105-1850, USA; kbailey@unmc.edu

Accepted 7 December 2019
Published Online First
21 January 2020

ABSTRACT

Patients with cystic fibrosis (CF) experience multiple pulmonary exacerbations throughout their lifetime, resulting in repeated antibiotic exposure and hospital admissions. Reliable diagnostic markers to guide antibiotic treatment in patients with CF, however, are lacking. Given that the CF airway is characterized by persistent and frequent bacterial infection, our goal was to determine if procalcitonin (PCT) could be used as a severity and prognostic marker of CF exacerbation. We enrolled 40 participants at the time of diagnosis of CF pulmonary exacerbation. Inclusion criteria: age ≥ 19 years with exacerbation requiring antibiotics as determined by the treating physician. Exclusion criteria: antibiotics initiated more than 48 hours prior to enrollment, and pregnancy. Blood samples were collected on enrollment day and after 7–10 days of treatment. Of the 40 patients enrolled, 23 (57.5%) had detectable levels of PCT (≥ 0.05 ng/mL). PCT levels were significantly associated with pulmonary exacerbation scores ($p=0.01$) and per cent decrease in forced expiratory volume in 1 second (FEV₁) ($p=0.01$) compared with the best in the last 12 months. Those who had worsening PCT during treatment had less improvement in FEV₁ ($p=0.001$) and were more likely to be readmitted to the hospital sooner ($p<0.0001$). Likewise, those who had a detectable PCT at the time of admission were more likely to be readmitted sooner ($p=0.03$). PCT elevation during antibiotic treatment is associated with less improvement in FEV₁ and earlier readmission. A detectable PCT level occurs only in more severe CF exacerbations. Multicenter trials are needed to confirm whether PCT may play a role in the clinical care of patients with CF.

INTRODUCTION

Patients with cystic fibrosis (CF) have periodic flare-ups or exacerbations of their chronic lung disease that are called CF pulmonary exacerbations. CF pulmonary exacerbations are associated with increased morbidity and mortality.¹ Those with more than 2 exacerbations/year have an increased risk of loss of lung function and death, or lung transplant.² Despite

Significance of this study

What is already known about this subject?

- ▶ Patients with cystic fibrosis (CF) have periodic exacerbations.
- ▶ Some, but not all, of these exacerbations are caused by bacteria.
- ▶ There is a need for a biomarker to help define exacerbations and guide treatment.

What are the new findings?

- ▶ Detectable levels of procalcitonin (PCT), a precursor to the hormone calcitonin, are associated with more severe CF pulmonary exacerbation, as measured by both a significant decrease in forced expiratory volume in 1 second and increase in readmissions, as well as by a C-reactive protein increase.
- ▶ An increase in PCT during treatment was associated with worsened outcomes.

How might these results change the focus of research or clinical practice?

- ▶ Further research is needed to determine whether PCT is a useful biomarker in adult CF exacerbations.

the importance of pulmonary exacerbations in the clinical course of CF, pulmonary exacerbations remain poorly defined in the literature. Most clinicians use a combination of clinical signs and symptoms along with spirometry and imaging to define exacerbations, however, there is not consensus between clinicians.^{3,4} Because of this lack of consensus, many have tried to define biomarkers of CF pulmonary exacerbations, but have been largely unsuccessful.⁵ One of the most studied biomarkers for CF pulmonary exacerbation is C-reactive protein (CRP). CRP is an acute phase reactant that is increased during CF pulmonary exacerbations, and decreased with antibiotic treatment.^{6,7} The CRP response, however, can be altered by treatment with steroids⁸ or chronic azithromycin,⁹ limiting its clinical utility. New biomarkers

© American Federation for Medical Research 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Bailey KL, Murphy PJ, Lineberry OK, et al. *J Invest Med* 2020;**68**:856–863.

Table 1 All participants

	n	%
Inpatient	37	92.5
Outpatient	3	7.5
Enrolled twice	7	17.5
Male	23	57.5
Female	17	42.5
Caucasian	40	100
Sputum culture positive for at least 1 strain of pseudomonas at admission	39	97.5
On oral steroids during admission	5	12.5
On chronic azithromycin	37	92.5
Antibiotics prescribed during the admission*	40	100
Tobramycin	24	60
Piperacillin/tazobactam	17	42
Vancomycin	13	32.5
Meropenem	11	27.5
Colistin	9	22.5
Cefepime	6	15
Aztreonam	6	15
Linezolid	4	10
Ciprofloxacin	4	10
Trimethoprim/sulfamethoxazole	1	2.5
	Mean±SD	
Age (y)	29.3±8.6	
BMI	21.6±3.4	
FEV ₁ at admission (% predicted)	47.2±20.2	
FEV ₁ at discharge (% predicted)	56.5±23.2	
Best FEV ₁ in the last 12 mo (L)	2.40±1.09	
Decline in FEV ₁ from the best in the last 12 mo (L)	0.67±0.43	
C-reactive protein (CRP) (mg/L)	4.0±3.8	
White cell count (×10 ⁹ /L)	11.89±5.10	
Serum procalcitonin (ng/mL) at admission	0.11±0.21	

*All patients were on 2 or more antibiotics.

BMI, body mass index; FEV₁, forced expiratory volume in 1 second.

are necessary to help guide diagnosis and treatment of CF pulmonary exacerbations.

Procalcitonin (PCT) is a precursor to the hormone calcitonin. In healthy adults, PCT is primarily made by the thyroid. In the presence of infection, other organs such as the lungs can produce PCT. This leads to an increase in PCT during invasive bacterial infections such as sepsis¹⁰ and pneumonia.¹¹ Because CF exacerbations often do not induce invasive bacterial infections, it is not clear whether PCT would be a helpful biomarker. It is clear that antibiotics are an effective treatment for CF exacerbations, and that changes in airway microbes occur during CF exacerbations.^{12–15} The optimal duration of intravenous antibiotics for CF pulmonary exacerbations is not known, but is a subject of current investigation. PCT also has been used as a biomarker to determine when to stop antibiotics.¹⁶

We hypothesized that PCT may be a useful biomarker in CF exacerbations to help stratify the severity of the exacerbation. To address this hypothesis, we measured serum PCT at the onset of CF exacerbation for 40 exacerbations.

Figure 1 Serum procalcitonin at the time of admission for cystic fibrosis (CF) pulmonary exacerbation correlates with C-reactive protein (CRP). Serum procalcitonin (ng/mL) and CRP levels (mg/L) were drawn at the time of admission for CF pulmonary exacerbation (n=40). There was a significant correlation between increasing CRP levels and increasing serum procalcitonin (p=0.0002).

METHODS

Recruitment of participants, inclusion and exclusion criteria

Participants were recruited prospectively between January 2012 and November 2013. Participants were followed for readmission until 2016. Individuals were eligible to participate if they were 19 years of age or older and were treated with intravenous antibiotics for a CF pulmonary exacerbation. The determination of the presence of exacerbation was determined by the clinician caring for the patient. In general, patients were diagnosed with an exacerbation if there was a significant decrease in their forced expiratory volume in 1 second (FEV₁) ($\geq 10\%$), an increase in shortness of breath, new or increased cough, decreased exercise tolerance, or change in sputum appearance. Treatment of the exacerbation was based solely on the discretion of the physician caring for the patient. These decisions were made by 2 physicians and were consistent through the course of the study. Participants were eligible for repeat enrollment if they had a second exacerbation during the study period. Subjects were excluded if they were pregnant, had antibiotic exposure (other than chronic azithromycin) in the 48 hours prior to enrollment or had a known infection of a non-lung site. If there was any possibility of pregnancy, a pregnancy test was performed prior to enrollment or antibiotic treatment. Pregnant patients were excluded because PCT is elevated during pregnancy.¹⁷

PCT measurements

For patients hospitalized for their exacerbation, blood was drawn for PCT measurement at the time of admission. For those who were treated as outpatients, blood was drawn at

Figure 2 Participants with a detectable procalcitonin (PCT) level (≥ 0.05 ng/mL) had higher C-reactive protein (CRP) levels. Participants with a detectable PCT (≥ 0.05 ng/mL) ($n=23$) measured at the time of admission had a 4.1-fold higher CRP level compared with those who had undetectable PCT levels ($n=17$). The mean is graphed with the SEM.

the time of diagnosis of the exacerbation. In a small subsegment of the population ($n=23$), a follow-up PCT level was drawn 7–10 days after treatment. The PCT levels were run in batches, and were not available to the treating physicians to make clinical decisions.

To measure PCT levels, serum was separated from whole blood using centrifugation. A commercially available sandwich ELISA was used to measure PCT following the manufacturer's directions (Vidas BRAHMS PCT). Briefly, 200 μ L of plasma was analyzed by the automated Vidas machine, which made measurements by the enzyme-dependent fluorescence method, and reported PCT levels ranging from 0.05 to 200 ng/mL. All samples with undetectable levels were recorded as 0.04 ng/mL.

Spirometry

Spirometry was performed at the time of admission and at the time of discharge. For those receiving outpatient intravenous antibiotics, spirometry was performed at the time of enrollment. Spirometry was performed in accordance to the American Thoracic Society guidelines.¹⁸ The National Health and Nutrition Examination Survey data set was used to determine the per cent predicted FEV_1 and forced vital capacity (FVC) based on age, height and weight.¹⁹ Per cent decrease in FEV_1 was calculated by subtracting

Figure 3 Higher procalcitonin (PCT) correlated with higher exacerbation scores. At the time of admission, we calculated a pulmonary exacerbation score (PES). The PES is a 14-element scoring system used at Akron Children's Hospital that consists of systemic and pulmonary signs and symptoms in conjunction with objective measurements of forced expiratory volume in 1 second (FEV_1), imaging and oxygen saturation. Higher scores indicate more severe exacerbations. PCT was statistically significantly higher in those with higher PES scores ($n=40$, $p=0.01$).

the admission FEV_1 (L) from the 'best' FEV_1 (L) in the last 12 months and dividing by the 'best' FEV_1 in the last 12 months. The per cent improvement in FEV_1 was calculated by subtracting the admission FEV_1 (L) from the discharge FEV_1 (L) and dividing by the discharge FEV_1 .

CF pulmonary exacerbation score

The severity of the CF exacerbation was estimated using the Akron Children's Hospital Pulmonary Exacerbation Score (PES).²⁰ This score assesses the following parameters: presence of fever, malaise, decrease in appetite, increased cough, sputum, dyspnea, chest exam, FEV_1 , and new chest X-ray findings. A higher score indicates a more severe exacerbation. Scores range from 0 to 15. This score was calculated by the admitting physician.

Data collection

We collected clinical data from the medical record, and an existing CF clinical database maintained by the CF center. We recorded the subject's 'best' FEV_1 and FVC in the year leading up to the admission. CRP levels and white cell counts were routinely collected at the time of admission and run by the clinical lab. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Nebraska Medical Center (UNMC). REDCap is a secure, web-based application designed to support data capture for research

studies. REDCap at UNMC is supported by the Research IT Office funded by the Vice Chancellor for Research and receives partial support from the Great Plains IDeA-CTR grant.

Statistical analysis

The statistical analysis and graphing were performed using Prism V.8 (GraphPad Prism software, La Jolla, CA). Two-way analysis of variance or unpaired t-tests were used for categorical data as appropriate. For continuous data, simple linear regression was used. Kaplan-Meier survival curves were compared using the log-rank (Mantel-Cox) test. A p value ≤ 0.05 was considered statistically significant.

RESULTS

Characteristics of the participants

Forty-three patients were approached about enrollment and 40 (93%) were enrolled. The characteristics of these subjects are summarized in [table 1](#). Most enrolled patients were hospitalized for their exacerbations (92.5%), while 3 (7.5%) were treated with intravenous antibiotics at home. Their average age was 29.3 ± 8.6 years, and 57.5% were male. Of the 40 patients enrolled, 23 (57%) had a detectable PCT level (0.05 ng/mL or greater). In 14 subjects, testing for respiratory viruses was performed. Of these, only 2 were positive, both for human rhinovirus, and both had undetectable PCT levels. Blood cultures were drawn in 12 subjects (29.3%) and all cultures were negative.

Of the 36 patients who had chest roentgenograms at the time of admission, 7 (19%) had new changes, which consisted of increased mucus plugging or new infiltrates. None of these were thought to be due to pneumonia. There were no differences in PCT levels between those with and without new chest imaging findings. The average PCT in those without new imaging changes was 0.11 ± 0.23 (n=29), those with new imaging changes had a PCT of 0.10 ± 0.05 (n=7, $p=0.87$). Only 1 subject (2.5%) was febrile at the time of admission. This subject had an elevated PCT of 1.31, white cell count of $7.8 \times 10^9/L$, and negative blood cultures. No cause for the fever besides severe CF pulmonary exacerbation was found. All participants had white cell counts performed at the time of admission. There was no correlation between white cell count and PCT level (n=40, $p=0.51$). There was also no correlation between body mass index (BMI) and PCT level (n=40, $p=0.69$).

PCT correlates with CRP levels

We measured CRP at the time of enrollment in 38 of the 40 participants. CRP is a marker of systemic inflammation, which has previously been shown to be increased in CF pulmonary exacerbations.²¹ We compared CRP to PCT levels at the time of enrollment and found a significant linear correlation ($p=0.002$) ([figure 1](#)). Likewise, when we analyzed only the participants who had detectable PCT levels (n=23), this linear correlation remained statistically significant ($p=0.01$). We also found that participants with detectable PCT (≥ 0.05 ng/mL) (n=23) had a statistically significantly higher CRP than those with an undetectable (<0.05) PCT (n=15) ($p=0.0007$). Those with undetectable PCT had a mean CRP of 1.5 ± 1.19 , while those with a

detectable PCT had a mean CRP of 6.11 ± 4.72 ($p=0.0007$) ([figure 2](#)).

PCT is higher in those with elevated PES

A PES was calculated based on the Akron Children's Hospital score. In this system, a higher PES score correlates with a more severe exacerbation.²⁰ There was a statistically significant increase in PES with increasing PCT at admission (n=40) ($p=0.01$) ([figure 3](#)). Likewise, when we analyzed only the participants who had detectable PCT levels (n=24), this linear correlation remained statistically significant ($p=0.02$).

Participants with larger decreases in FEV₁ had higher PCT levels

All participants had spirometry performed at the time of admission. We compared their FEV₁ at the time of admission to their highest FEV₁ in the past 12 months, and calculated the per cent decrease in FEV₁. The per cent changes ranged from 0% to 60% decline. We compared those with a 0%–29% decline in FEV₁ (n=23) to those with a 30%–60% decline in FEV₁ (n=17). We found that those with a 0%–29% change had a significantly lower mean PCT of 0.06 ± 0.007 , while those with a 30%–60% decline had a mean PCT of 0.19 ± 0.07 ($p=0.01$) ([figure 4](#)).

PCT had variable changes after treatment

In a subset of participants (n=23) we recorded a PCT level at admission as well as after 7–10 days of treatment with intravenous antibiotics. Most PCT levels decreased or did not change with treatment (73.9%, n=17), however, 6 participants (26%) had an increase in PCT after treatment ([figure 5](#)). There is no statistically significant difference between the day 0 and day 7–10 PCT ($p=0.25$).

Those with an increase in PCT after treatment had less improvement in their FEV₁

A small number of patients (n=6) had an increase in PCT after treatment. The demographics of these patients are included in [table 2](#). In general, their characteristics were very similar to the demographics of the patients who had no change or a decrease in their PCT over time. Notable differences include that 100% of the participants who had increasing PCT after treatment had detectable PCT at admission, compared with 35% of those who had no change or a decrease in PCT. Also of interest, those who had an increase in their PCT after treatment had higher CRP at admission 7.90 ± 4.2 mg/L vs 3.25 ± 3.5 mg/L ($p=0.02$) in those who had stable or decreasing PCT with treatment. Antibiotics used were also very similar, with the exception of an increase in meropenem use in the increasing PCT group ($p=0.05$).

We compared those who had an increase in PCT after treatment with those who had a decrease or no change in PCT. Those who had no change or a decrease in PCT had a 27.9% improvement in FEV₁ whereas those who had an increase in PCT had only a 4.9% improvement in FEV₁, with 2 participants having a worsening of FEV₁ after treatment ($p=0.001$) ([figure 6](#)).

Table 2 Participants who had no change in PCT (n=17) compared with those with increasing PCT (n=6)

	No change or decreasing PCT (n=17)	Increasing PCT (n=6)	P value
Inpatient	17 (100%)	6 (100%)	1.0
Outpatient	0 (0%)	0 (0%)	1.0
Male	10 (59%)	3 (50%)	1.0
Female	7 (41%)	3 (50%)	1.0
Caucasian	17 (100%)	6 (100%)	1.0
Sputum culture positive for at least 1 strain of pseudomonas at admission	17 (100%)	6 (100%)	1.0
On oral steroids during admission	1 (5.9%)	2 (33.3%)	0.23
On chronic azithromycin	16 (94%)	5 (83%)	0.46
Antibiotics prescribed during the admission	17 (100%)	6 (100%)	1.0
Tobramycin	10 (58.8%)	4 (66.6%)	1.0
Piperacillin/tazobactam	11 (64.7%)	1 (16.6%)	0.06
Vancomycin	4 (23.5%)	3 (50%)	0.66
Meropenem	3 (17.6%)	4 (66%)	0.05
Colistin	4 (23.5%)	2 (33%)	0.63
Cefepime	3 (17.6%)	0 (0%)	0.53
Aztreonam	0 (0%)	1 (16.6%)	0.26
Linezolid	1 (5.8%)	0 (0%)	1.0
Ciprofloxacin	1 (5.8%)	0 (0%)	1.0
Trimethoprim/sulfamethoxazole	1 (5.8%)	0 (0%)	1.0
	Mean±SD	Mean±SD	P value
Age (y)	27.0±5.1	30±9.0	0.07
BMI	20.38±1.84	20.5±1.65	0.88
FEV ₁ at admission (% predicted)	48.94±25.1	38.15±11.3	0.32
C-reactive protein (CRP) (mg/L)	3.25±3.5	7.90±4.2	0.02
White cell count (×10 ⁹ /L)	13.21±6.62	12.43±4.2	0.79
Serum procalcitonin (ng/mL) at admission	0.07±0.05	0.09±0.04	0.25

*All patients were on 2 or more antibiotics.

Bolded values are statistically significant.

BMI, body mass index; FEV₁, forced expiratory volume in 1 second; PCT, procalcitonin.

Those with an increase in PCT after treatment or a detectable PCT at admission were readmitted sooner

We followed participants for 2 years to determine the time of their next admission for a pulmonary exacerbation. In those who had an increase in PCT after treatment (n=6), the median time to admission was 57.5 days with all participants being readmitted within 100 days. In those who had a PCT that decreased or stayed the same (n=17), the median time to readmission was 175.5 days (figure 7). These differences were statistically significant (p<0.0001). Given the interesting data that an increase in PCT after treatment predicted an earlier readmission, we examined whether a detectable PCT (≥0.05 ng/mL) at admission predicts days to readmission (figure 8). Of the 40 participants, 23 had undetectable PCT at admission and 17 had a detectable PCT. The median time to readmission in the undetectable PCT group was 210 days, while in the detectable PCT group the median time to readmission was 84 days, a statistically significant difference (p=0.03). We also analyzed whether

Figure 4 Those with a greater percentage decrease in forced expiratory volume in 1 second (FEV₁) had higher procalcitonin levels. We divided patients into 2 groups. One that had a 0%–29% decrease in their FEV₁ at the time of admission for exacerbation and those that had a 30%–60% decrease in FEV₁. The participants with the larger % decrease in FEV₁ had higher procalcitonin levels. PCT, procalcitonin.

CRP level at admission was associated with readmission time (figure 9). There was a trend towards elevated CRP correlating with earlier readmission, however, this was not statistically significant (p=0.053).

DISCUSSION

In this study, we demonstrated that detectable levels of PCT are associated with more severe CF pulmonary exacerbation, as measured by decrease in FEV₁ and increase in readmissions. In addition, an increase in PCT during antibiotic treatment was associated with worsened outcomes.

Previous publications have measured PCT in patients with CF. For instance, in children with CF, PCT is not elevated at baseline or with exacerbation. Louw *et al* measured PCT in 92 children at baseline, and measured no elevation in PCT at baseline. They also measured PCT at the time of admission for 33 CF exacerbations and found no elevation in PCT.²² In adult patients with CF, Loh *et al* showed that PCT is not elevated in CF exacerbations in a cohort of 17 adult patients.²³ In our study, PCT was detectable in roughly half of the CF exacerbations. Importantly, these were the more severe CF pulmonary exacerbations.

In contrast to the studies performed in children, our adult cohort had moderately severe CF lung disease, with

Figure 5 Procalcitonin varies after treatment for cystic fibrosis (CF) exacerbation. A subset of participants ($n=23$) had a follow-up procalcitonin level 7–10 d after treatment with antibiotics. Most had a decrease or no change in the procalcitonin (PCT) after treatment ($n=17$), while 6 participants had an increase in their PCT after treatment. There was no statistical difference between the PCT before and after treatment ($p=0.25$).

Figure 6 Participants with an increase in procalcitonin after treatment for an exacerbation had less improvement in their % forced expiratory volume in 1 second (FEV_1). The participants who had a decrease or no change in their procalcitonin (PCT) ($n=17$) after treatment had a better improvement in their FEV_1 after treatment compared with those who had an increase in their PCT ($n=6$) ($p=0.001$).

low BMI (mean 21.6), low FEV_1 at admission (47.2% predicted) and nearly universal sputum cultures positive for pseudomonas (97.5%). In this population, we found that even small elevations in PCT may be important clinically in CF. In fact, having a PCT that is detectable (≥ 0.05 ng/mL), much lower than the 0.25 ng/mL cut-off for invasive bacterial infection, seemed to have clinical significance. For instance, patients with a detectable PCT (≥ 0.05 ng/mL) predicted higher levels of systemic inflammation such as CRP (figure 2). Participants who had a detectable PCT at the beginning of an exacerbation were more likely to be readmitted sooner for a respiratory exacerbation (figure 8). In addition, the trajectory of the PCT level during the exacerbation was important. If PCT increased during the exacerbation, participants had very little improvement in FEV_1 (figure 6), and were likely to be readmitted sooner (figure 7). Those who had more severe exacerbations were more likely to have higher PCT levels. For instance, PCT levels correlated with PES (figure 3), CRP levels (table 1) and larger decreases in per cent FEV_1 (figure 4). A similar prognostic value of PCT has also been seen in patients with community-acquired pneumonia presenting to the emergency room. In a recent meta-analysis of 14 trials including

Figure 7 Participants with an increase in procalcitonin (PCT) after treatment were readmitted. All of the patients who had an increase in their PCT after treatment were readmitted within 100 d of discharge. Those with PCT that was decreased or unchanged had a significantly longer period of time to readmission ($p<0.0001$).

Figure 8 Procalcitonin (PCT) at the time of admission may predict an earlier readmission. Participants with a detectable PCT (≥ 0.05 ng/mL) at the time of admission were readmitted sooner than those with undetectable PCT (< 0.05 ng/mL). This was statistically significant with $p=0.03$.

Figure 9 C-reactive protein (CRP) at the time of admission does not predict readmission. Time to readmission was analyzed for those with an elevated CRP (≥ 3.0 mg/L) at admission ($n=22$), and those with a normal CRP (< 3.0 mg/L) at admission ($n=18$). There was a strong trend towards significance with $p=0.053$.

4211 patients, elevated PCT levels were associated with increased risk of treatment failure and mortality.²⁴

The traditional cut-off for suspecting systemic bacterial infection with PCT is 0.25 ng/mL. This level is not reached for most patients with CF pulmonary exacerbations. However, slight elevations of PCT, like we measured, may be reflective of low-grade invasive bacterial infections. For example, some have postulated that low PCT levels may indicate bacterial colonization, while higher levels of PCT indicate more invasive infections that are activating the innate immune system.²⁵ In the case of CF, elevations in serum PCT may indicate that there is a breakdown in the integrity of the airway epithelium, allowing bacteria to create a more invasive infection and activate the innate immune system. A similar small increase in PCT was seen in adults with non-CF bronchiectasis that required inpatient treatment with antibiotics. In that study, the average

outpatient PCT was 0.03, and increased to 0.102 with need for antibiotics.²⁶

In our study, clinicians were blinded to PCT levels, so that their care was not affected by them. However, PCT levels have the potential to help guide when antibiotics can safely be stopped in CF pulmonary exacerbations. Increasing PCT levels may also provide an indication that antibiotic coverage should be changed. The optimal length of treatment for CF exacerbations is currently unknown. The Standardized Treatment of Pulmonary Exacerbations 2 trial is currently attempting to determine the optimal duration of antibiotic therapy.²⁷ CF pulmonary exacerbations, however, are heterogeneous in nature,²⁸ and more sensitive biomarkers are needed to assist clinicians in determining the optimal duration of therapy. Limitations of our study include the small sample size. However, our sample size was able to detect several statistically significant effects. Another limitation is the fact that all patients were recruited from a single center, so our findings will need to be further evaluated by multicenter trials. In addition, we did not obtain CRP levels after treatment to determine if they increased or decreased in conjunction with PCT.

In conclusion, PCT has the potential to develop into a biomarker that is useful in the management of CF pulmonary exacerbations. Our pilot study shows the potential utility of the biomarker to help determine the severity of the exacerbation, and prognosticate about the success of treatment. In particular, a rising PCT during antibiotic treatment is ominous, predicting less improvement in FEV₁ with treatment, and earlier readmission. Future multicenter trials are required to determine whether PCT may play a role in the clinical care of CF pulmonary exacerbations.

Contributors KLB assisted with study design, drafted, edited and approved the manuscript, oversaw writing and submission of the IRB protocol, consented patients, and analyzed the data. PJM edited and approved the manuscript, consented patients, and analyzed the data. OKL and MRH edited and approved the manuscript, helped write and submit the IRB protocol, consented patients, performed clinical assessments, generated data, and analyzed the data. JDD drafted, edited and approved the manuscript, and analyzed the data. ACK performed the procalcitonin assays, assisted with study design, drafted, edited and approved the manuscript, and analyzed the data.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Deidentified participant data from which the figures are composed are available upon reasonable peer request.

ORCID iD

Kristina L Bailey <http://orcid.org/0000-0003-2990-9042>

REFERENCES

- Sanders DB, Bittner RCL, Rosenfeld M, et al. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med* 2010;182:627–32.
- de Boer K, Vandemheen KL, Tullis E, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. *Thorax* 2011;66:680–5.
- Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med* 2009;180:802–8.
- Bilton D, Canny G, Conway S, et al. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working

- group on outcome parameters in clinical trials. *J Cyst Fibros* 2011;10(Suppl 2):S79–81.
- 5 Shoki AH, Mayer-Hamblett N, Wilcox PG, *et al.* Systematic review of blood biomarkers in cystic fibrosis pulmonary exacerbations. *Chest* 2013;144:1659–70.
 - 6 Glass S, Hayward C, Govan JR. Serum C-reactive protein in assessment of pulmonary exacerbations and antimicrobial therapy in cystic fibrosis. *J Pediatr* 1988;113:76–9.
 - 7 Friesen CA, Wiens LA, Burry VF, *et al.* C-Reactive protein in acute pulmonary exacerbations of patients with cystic fibrosis. *Pediatr Pulmonol* 1995;20:215–9.
 - 8 Smith JW, Colombo JL, McDonald TL. Comparison of serum amyloid A and C-reactive protein as indicators of lung inflammation in corticosteroid treated and non-corticosteroid treated cystic fibrosis patients. *J Clin Lab Anal* 1992;6:219–24.
 - 9 Wolter J, Seeney S, Bell S, *et al.* Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax* 2002;57:212–6.
 - 10 Assicot M, Gendrel D, Carsin H, *et al.* High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* 1993;341:515–8.
 - 11 Christ-Crain M, Stolz D, Bingisser R, *et al.* Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia. *Am J Respir Crit Care Med* 2006;174:84–93.
 - 12 Tunney MM, Klem ER, Fodor AA, *et al.* Use of culture and molecular analysis to determine the effect of antibiotic treatment on microbial community diversity and abundance during exacerbation in patients with cystic fibrosis. *Thorax* 2011;66:579–84.
 - 13 Price KE, Hampton TH, Gifford AH, *et al.* Unique microbial communities persist in individual cystic fibrosis patients throughout a clinical exacerbation. *Microbiome* 2013;1.
 - 14 Carmody LA, Zhao J, Schloss PD, *et al.* Changes in cystic fibrosis airway microbiota at pulmonary exacerbation. *Ann Am Thorac Soc* 2013;10:179–87.
 - 15 Carmody LA, Zhao J, Kalikin LM, *et al.* The daily dynamics of cystic fibrosis airway microbiota during clinical stability and at exacerbation. *Microbiome* 2015;3.
 - 16 de Jong E, van Oers JA, Beishuizen A, *et al.* Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 2016;16:819–27.
 - 17 Paccolat C, Harbarth S, Courvoisier D, *et al.* Procalcitonin levels during pregnancy, delivery and postpartum. *J Perinat Med* 2011;39:679–83.
 - 18 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
 - 19 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–87.
 - 20 Kraynack NC, McBride JT. Improving care at cystic fibrosis centers through quality improvement. *Semin Respir Crit Care Med* 2009;30:547–58.
 - 21 Horsley AR, Davies JC, Gray RD, *et al.* Changes in physiological, functional and structural markers of cystic fibrosis lung disease with treatment of a pulmonary exacerbation. *Thorax* 2013;68:532–9.
 - 22 Louw JJ, Toelen J, Proesmans M, *et al.* Serum procalcitonin is not an early marker of pulmonary exacerbation in children with cystic fibrosis. *Eur J Pediatr* 2012;171:139–42.
 - 23 Loh G, Ryaboy I, Skabelund A, *et al.* Procalcitonin, erythrocyte sedimentation rate and C-reactive protein in acute pulmonary exacerbations of cystic fibrosis. *Clin Respir J* 2018;12:1545–9.
 - 24 Kutz A, Briel M, Christ-Crain M, *et al.* Prognostic value of procalcitonin in respiratory tract infections across clinical settings. *Crit Care* 2015;19:74.
 - 25 Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol* 2010;48:2325–9.
 - 26 Loebinger MR, Shoemark A, Berry M, *et al.* Procalcitonin in stable and unstable patients with bronchiectasis. *Chron Respir Dis* 2008;5:155–60.
 - 27 Heltshe SL, West NE, VanDevanter DR, *et al.* Study design considerations for the standardized treatment of pulmonary exacerbations 2 (STOP2): a trial to compare intravenous antibiotic treatment durations in CF. *Contemp Clin Trials* 2018;64:35–40.
 - 28 BURGEL P-R, Reid DW, Aaron SD. A first step to STOP cystic fibrosis exacerbations. *J Cyst Fibros* 2017;16:529–31.