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Relationship of Pulmonary Outcomes, Microbiology, and Serum Antibiotic Concentrations in Cystic Fibrosis Patients

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OBJECTIVES To determine the frequency of subtherapeutic exposure to intravenously administered β-lactam antibiotics in a cohort of cystic fibrosis (CF) patients who were treated for a pulmonary exacerbation, and its impact on pulmonary function.

METHODS Nineteen CF patients between the ages of 5 and 21 years treated at Children's National Health System for a pulmonary exacerbation were followed between March 2015 and August 2016 in a prospective, longitudinal study. Pharmacokinetic modeling and minimum inhibitory concentrations (MICs) of the involved pathogens were used to determine therapeutic or subtherapeutic β-lactam antibiotic exposure based on the time the antibiotic concentration was above the MIC. Clinical outcomes were measured by spirometry values.

RESULTS The 19 participants were treated with a total of 29 courses of antibiotics. The most common β-lactam antibiotics used in a treatment course were ceftazidime (62%) and meropenem (45%). There was no difference in age, CF genotype, or creatinine clearance between the 9 participants (47%) who reached therapeutic concentrations versus the 10 (53%) who did not. Those who achieved sufficiently high antibiotic exposure had more significant improvement of their pulmonary function tests.

CONCLUSIONS We found that sufficient antibiotic exposure during treatment of CF pulmonary exacerbations was associated with improved pulmonary function. Moreover, it was impossible to predict, solely from the dosing regimen used, which patients were going to reach therapeutic β-lactam antibiotic serum concentrations. This suggests that CF patients may benefit from closer monitoring of their β-lactam exposure and bacterial MIC for optimal clinical outcomes.

ABBREVIATIONS CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; FDA, US Food and Drug Administration; $FEF_{25–75}$, forced expiratory flow at 25% to 75%; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IV, intravenous; LC-MS, liquid chromatography mass spectroscopy; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; T > MIC, time above the minimum inhibitory concentration

KEYWORDS beta-lactams; cystic fibrosis; pediatrics; pharmacodynamics; pulmonary

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Introduction

Cystic fibrosis (CF) is an autosomal recessive disease that leads to significant morbidity and mortality among those affected.[1] Disease is most significant in the pulmonary system, with thick fluid secretions, bacterial infections, inflammation, and bronchiectasis.[2] The best way to select antibiotic treatment for these infections is still unclear because some studies have shown clinical improvement despite the presence of underlying antibiotic resistance.[3] However, current recommendations for the treatment of acute pulmonary exacerbations are to use antibiotic therapy directed toward specific pathogens identified in culture-based techniques.[4]

Management of mild pulmonary exacerbations is generally performed with oral and/or aerosolized antibiotics, whereas treatment of severe exacerbations often includes intravenous (IV) antibiotic therapy with a combination of at least 2 unique-mechanism drugs.[4] Other factors that influence the use of IV antibiotics include a patient's age, underlying disease progression, and baseline pulmonary function.[5] Given the limited number of antibiotics, particularly those capable of treating the prevalent and virulent organism *Pseudomonas aeruginosa*, drug resistance and efficacy are of particular concern. Furthermore, exacerbations lead to a reduction in long-term pulmonary function.[6] The continuous threat of antibiotic resistance, combined

with the acute and long-term impact on disease progression, lung function, and quality of life, heightens the importance of effective treatment of exacerbations with antibiotic therapy.

Current management of severe exacerbations is most often a combination of an antipseudomonal β-lactam antibiotic and an aminoglycoside.[4,7,8] β-Lactam antibiotics are time dependent in their bactericidal activity; thus, in order to achieve maximal efficacy, β-lactam antibiotic serum concentrations need to be above the minimum inhibitory concentration (MIC) for a certain period of time. This T > MIC has been estimated to be ≥40% for carbapenems, ≥50% for penicillins, and ≥60% to 70% for cephalosporins.[9-15]

Because of altered renal clearance and increased incidence of antibiotic resistance in the CF population, antibiotic treatment during pulmonary exacerbations requires revised dosing strategies given pharmacokinetics (PK) among the CF population.[16] Using these principles, new dosing strategies have been developed to improve drug efficacy.[9,10] Furthermore, using population PK modeling and individualized data, one can predict the likelihood of a particular antibiotic course achieving optimal therapeutic pharmacodynamics (PD) markers for every individual patient.[17]

Although updated Cystic Fibrosis Foundation (CFF) and European consensus guidelines suggest larger dosing regimens to overcome more rapid renal clearance, recent surveys on antipseudomonal β-lactam use found that the dosing regimens used in 38% to 53% of the CF centers are actually below these guidelines.[7,18–20]

Prior studies have shown that some CF patients improve with antibacterial therapy, even when treating antibiotic-resistant organisms.[3] This affects clinical practice, because some providers may choose to continue antibiotics despite reported resistance, if the patient shows clinical improvement. Based on the aforementioned large variation in dosing regimens used, we hypothesized that the impact of antibacterial therapy, even in the presence of bacteria with higher MICs, will be dependent upon the achieved PD.

Therefore, our primary objective was to determine the impact of reaching only subtherapeutic β-lactam antibiotic exposure on the recovery of pulmonary function in children with CF receiving IV β-lactam antibiotics for treatment of acute pulmonary exacerbations.

Materials and Methods

Setting and Study Population. This prospective 18-month longitudinal study was conducted at the Children's National Health System (a tertiary-care hospital with an accredited CF Center serving the greater metropolitan Washington, DC, area) after receiving Institutional Review Board approval. The principles outlined in the Declaration of Helsinki were followed. Written informed consent was obtained from study participants ages ≥18 years, and parental permission was obtained for those ages <18 years. Assent was obtained from study participants ages 7 to 17 years. Enrollment was limited to those who had been hospitalized for IV antibiotics in the 3 years prior, because they were deemed most likely to receive IV antibiotics during the study period.

Patient Encounters. The study consisted of 4 different periods of evaluation ("encounters"). The first evaluation (encounter 1) occurred when the patients were in their usual state of health and at least 30 days after they had received a therapeutic course of antibiotics (they were allowed to take their maintenance inhaled and/or oral antibiotics). The second evaluation (encounter 2) was in the beginning of an acute pulmonary exacerbation requiring IV antibiotic therapy (either in the hospital or at home). The third evaluation (encounter 3) was at the end of the treatment of pulmonary exacerbation, and the fourth evaluation (encounter 4) occurred more than 30 days after the treatment course was completed. In each encounter, the patient provided respiratory samples (expectorated sputum or deep throat culture). For encounter 2, the respiratory culture was obtained on day 0. For encounter 3, respiratory cultures were obtained the day before completion of antibiotic therapy for participants receiving ≤7 days of therapy, and were obtained at least >7 days after initiation of antibiotic therapy for participants receiving longer courses. In addition, during encounters 2 and 3 blood samples were obtained to calculate the PK of the infused antibiotics.[21]

Pulmonary function tests were obtained as ordered by the primary team, but they typically occurred on day 0 of the exacerbation and once a week thereafter until antibiotics were discontinued. The last set of pulmonary function tests obtained before stopping antibiotic therapy was used in the analysis. Results were reported using NHANES III reference values.[22] For our primary outcome, we were most interested in improvement of forced expiratory volume in 1 second (FEV_1) % predicted, and forced expiratory flow at 25% to 75% ($FEF_{25–75}$) % predicted, because they measure flow in the larger and smaller airways, respectively. Based on our hypothesis, we also were most interested in the improvement in pulmonary function from exacerbation to end of treatment (encounters 2 to 3) and from exacerbation to follow-up (encounters 2 to 4). We measured the difference between encounters to accommodate for variation in baseline pulmonary function among the study participants.

Pulmonary exacerbations were defined as a change in at least 4 of the following 12 signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; fever >38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical exam of the chest; decrease in FEV_1 % predicted by 10%, or radiographic changes of the chest.[23] For inclusion in the study, participants also had to be

prescribed at least 1 IV β-lactam antibiotic. Study participants who experienced more than 1 pulmonary exacerbation requiring IV antibiotics during the study period were asked to participate for each treatment course.

Data Collection. Study data were collected and managed using REDCap electronic data capture tools hosted at the Children's National Medical Center.[24] The following data were collected during each encounter: age, sex, race/ethnicity, CF transmembrane conductance receptor genotype, weight, height, medications, and spirometry values (FEV_1 % predicted, forced vital capacity [FVC], FEV_1/FVC ratio, and $FEF_{25–75}$ % predicted). FEV_1 % predicted was used to determine lung disease stage and aggressiveness.[25] Cystic fibrosis disease was considered early if FEV_1 % predicted was ≥70%, intermediate if <70% but ≥40%, and advanced if <40%. Cystic fibrosis aggressiveness evaluates FEV_1 % predicted as a function of age, and is categorized as mild, moderate, and severe. History of antibiotic resistance was also noted, and was defined as growing a pathogen resistant to antibiotics within at least 1 drug class typically used for treatment.

For each pulmonary exacerbation, information was also collected on the antibiotics given and whether steroids were administered. The MIC break points for antibiotics of bacteria grown by conventional culture techniques were used for determination of T > MIC. The clinical microbiology laboratory used MicroScan (Beckman Coulter, Brea CA) broth dilution to perform susceptibility testing of CF respiratory samples, with a validated protocol for mucoid *P aeruginosa*. For antibiotic-resistant bacteria (e.g., piperacillin-tazobactam MIC >64), the break point was used (e.g., MIC 64) for the calculation of T > MIC.

Antibiotic Concentrations. Plasma drug concentrations of IV β-lactam antibiotics were obtained during the treatment course. Sample collection began after the patient had been on antibiotic therapy >24 hours to ensure he or she had achieved steady state. The protocol called for sample collection a minimum of 4 time points: a trough <30 minutes before a dose, a peak 1 hour after the dose was infused, a sample 3 to 4 hours after the dose was infused, and a repeat trough <30 minutes before another dose. A random drug concentration was also obtained at the end of the antibiotic treatment course when possible. If 2 β-lactam antibiotics were being administered, the blood draws were timed based on the dosing schedule of one of these antibiotics. To maintain concentration integrity, specimens were processed immediately and then frozen at −80°C. Specimens were shipped on dry ice to the Pharmaco-Analytical laboratory (University of Southern California), and placed in the freezer upon arrival. While conducting the assay, specimens were placed in ice until they were transferred to conduct the multiplex liquid chromatography mass spectroscopy assay at 4°C. Plasma concentrations for ceftazidime, imipenem, piperacillin, and meropenem were determined from each sample.

PK Modeling. The PK modeling of β-lactam antibiotics was performed using Bayesian estimation in MW/Pharm (version 3.80, Mediware, Prague Czech Republic).[17,26] Parameters used to model the full antibiotic course included patient age, weight, height, serum creatinine, and plasma concentrations when available. Each antibiotic dose was entered into the model based on the time it was received per nursing documentation, and incorporated drug infusion time. Organism identification and the antibiotic MIC targeted for the PD determination were collected from the patient's concurrent clinical respiratory culture results. To determine whether an antibiotic course was therapeutic for Gram-negative bacteria, the T > MIC at 3 different dosing intervals after achieving steady state (>24 hours) was calculated and averaged.[15] If the culture grew more than 1 Gram-negative bacterium, the highest MIC was used. If the culture grew *Staphylococcus aureus*, MICs reported in the literature for MSSA were used, because our laboratory does not report MICs for the β-lactams used in this study.[27,28] If the respiratory culture grew MRSA, the patient had to also be on MRSA-directed therapy (linezolid or vancomycin with troughs >10 mg/L) so as to not misclassify any participants. If the culture did not grow a pathogen for which to extrapolate an MIC, antibiotic exposure was evaluated against the median MIC for isolates from the 8 study patients who grew *P aeruginosa*, because β-lactam therapy is typically selected to target this organism. Aminoglycosides were also used in most participants, and those intravenously administered were always adjusted to meet therapeutic concentrations per clinical care guidelines at our institution (e.g., tobramycin dosed every 24 hours with 1-hour peak goals of 20–30 mg/L and trough goals of ≤1 mg/L; amikacin dosed every 24 hours with 1-hour peak goals of 30–45 mg/L and trough goals of ≤5 mg/L).

Statistical Analysis. Risk ratios and *t* test were used to assess baseline patient characteristics. Non-parametric alternatives were also evaluated but showed no significant change in p values.

Risk ratios with 95% confidence interval and *t* test were also used to compare measures that varied by exacerbation. Generalized estimating equations were used in the statistical analysis to account for the repeated exacerbations within patients. For our primary outcome (change in pulmonary function), the change between a pair of encounters was used to accommodate for any differences in baseline lung function between study participants.

Results

Baseline Clinical Data. A total of 19 study participants were enrolled between March and November 2015 and followed prospectively through August 2016. These 19 participants were treated with 29 courses of IV antibiot-

Table 1. Study Participant Baseline Characteristics and Potential Risk Factors for Subtherapeutic β-Lactam Antibiotic Exposure*

	Subtherapeutic (n = 9)	Therapeutic (n = 10)	Risk Ratio (95% CI)
Sex, male, n (%)	6 (67)	7 (70)	0.95 (0.52–1.76)
Race, white n (%)	3 (33)	6 (60)	0.56 (0.19–1.59)
CFTR mutation, n (% F508del homozygous)	3 (34)	3 (30)	1.11 (0.30–4.17)
CFTR mutation, n (% F508del heterozygous or homozygous)	7 (78)	7 (70)	1.11 (0.65–1.90)
CFTR potentiator, n (% yes)	2 (22)	2 (20)	1.11 (1.14– 6.34)
Insulin-dependent CF-related diabetes, n (% yes)	1 (11)	2 (20)	0.56 (0.06–5.14)
Suppressive oral antibiotics, n (% yes)	7 (78)	6 (60)	1.30 (0.70–2.40)
Suppressive inhaled antibiotics, n (% yes)	9 (100)	5 (50)	2.00 (1.08–3.72)
Antibiotic resistance, n (% yes)	1 (11)	3 (30)	0.37 (0.05–2.95)
Disease stage, n (% intermediate/advanced)	4 (44)	2 (20)	2.22 (0.52–9.37)
Disease aggressiveness, n (% moderate/severe)	8 (89)	7 (70)	1.23 (0.80–2.03)

CF, cystic fibrosis; CFTR, CF transmembrane conductance receptor

* The first exacerbation for each patient (note of the 19 patients, for those with multiple exacerbations, only 1 was considered therapeutic and subtherapeutic in separate antibiotic courses).

ics. Thirteen CF patients experienced 1 exacerbation, whereas 4 had 2 exacerbations, 1 had 3 exacerbations, and 1 had 5 exacerbations. The 2 participants with more than 2 pulmonary exacerbations during the study period had severe disease aggressiveness, with 1 having intermediate and 1 having advanced disease stage. Of the 4 participants with 2 exacerbations, all had early disease stage, whereas 3 had mild and 1 had intermediate disease aggressiveness. When comparing patient characteristics at their first exacerbation, there was no significant difference in the age of the patient (therapeutic mean age 11.3 [SD 5.00] versus subtherapeutic mean age 13.22 [SD 5.37], p = 0.458). Other potential baseline risk factors for subtherapeutic antibiotic exposure are shown in Table 1. Participants receiving suppressive inhaled antibiotics at baseline were more likely to have subtherapeutic β-lactam antibiotic exposure (RR 2.00, 95% CI 1.08–3.72). It should also be noted that sample sizes were small and that, although not significant, participants who reached subtherapeutic concentrations tended to be more likely to do so in later stages of their disease (RR 2.22, 95% CI 0.52–9.37; see Table 1 and Figure 1).

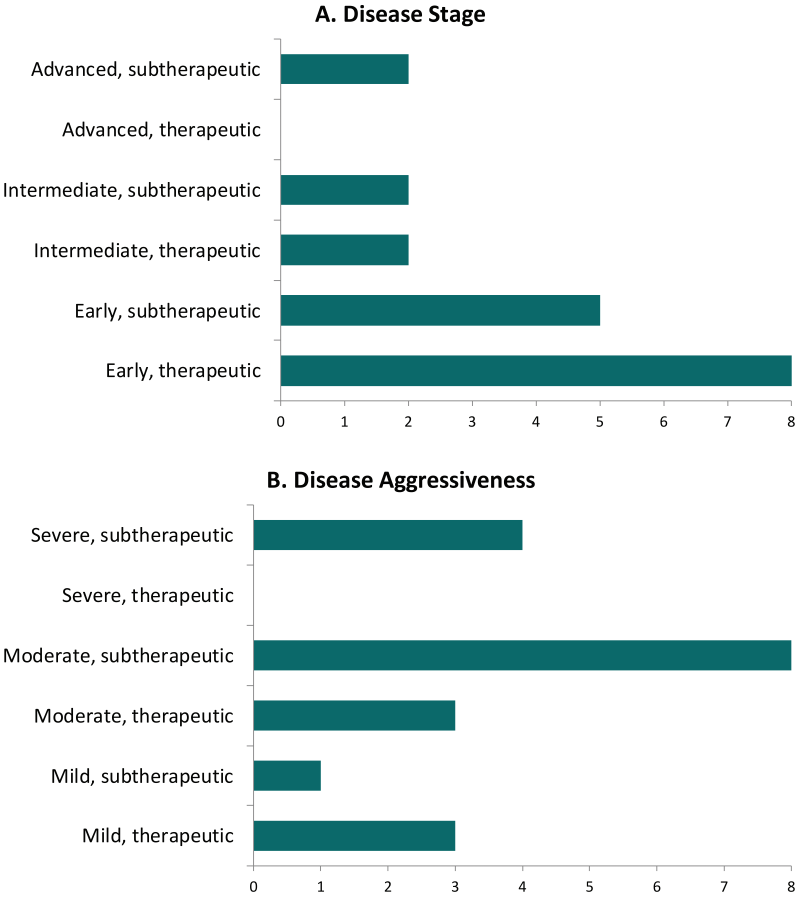
Exacerbation Culture Data. During pulmonary exacerbations (n = 29), 45% of respiratory cultures grew 1 pathogen, 31% grew more than 1 pathogen, and 24% did not grow any pathogens. The most commonly cultured pathogens were *S aureus* (37.9%) and *P aeruginosa* (27.6%). For any given culture, the highest MIC reported for all Gram-negative pathogens present was noted. The median values relative to the β-lactam antibiotics used for treatment are shown in Table 2.

Antibiotic Use and Determination of β-Lactam PK. The most common antibiotics included for >72 hours in an individual regimen (n = 29) were tobramycin (66%), ceftazidime (62%), meropenem (45%), and piperacillin-tazobactam (17%). All IV antibiotics were given via intermittent infusion. The most common empiric antibiotic combinations started at admission were ceftazidime and tobramycin (38%), followed by meropenem and tobramycin (14%).

Of the 29 antibiotic treatment regimens used for pulmonary exacerbations, a total of 38 antipseudomonal β-lactam antibiotics were used for >72 hours. In 5 treatment courses, 2 β-lactam antibiotics were administered concurrently; in 1 course, 3 β-lactam antibiotics were administered concurrently. Ceftazidime (n = 18), meropenem (n = 13), piperacillin-tazobactam (n = 5), imipenem-cilastatin (n = 1), and aztreonam (n = 1) were evaluated using PK modeling. All β-lactam antibiotics were intermittently dosed, and none were given via extended or continuous infusion. Calculated midinterval concentrations from the population PK models for participants achieving therapeutic concentrations and those achieving subtherapeutic concentrations are shown in Table 2 and Figure 2. The midinterval concentrations of ceftazidime and piperacillin-tazobactam in the therapeutic group tended to be higher than those in the subtherapeutic group. This was not true for meropenem; the midinterval concentrations appeared to be more similar in both groups.

Determination of Therapeutic Versus Subtherapeutic Antibiotic Exposure Using β-Lactam PD. Antibiotic treatment courses (n = 29) were divided into therapeutic or subtherapeutic groups based on their β-lactam exposure. Participants on more than 1 β-lactam were deemed therapeutic if at least 1 of the antibiotics achieved a sufficient T > MIC. When the patient had a culture that grew

Figure 1. Disease stage and severity. Disease stage (A) and aggressiveness (B) according to plotting FEV_1 % predicted.[25] Disease stage is a measure of FEV_1 % predicted alone, with ≥70% considered early, 70% < *x* ≥ 40% considered intermediate, and <40% considered advanced. Disease severity, categorized as mild, moderate, and severe, is measured by FEV_1 % predicted as a function of age. *FEV_1, forced expiratory volume in 1 second*.



a Gram-negative pathogen, the reported MIC for the antibiotic received was used. If the patient grew more than 1 Gram-negative pathogen, the highest reported MIC was used. When MICs were at the upper limit of detection (e.g., ceftazidime MIC >16 or piperacillin-tazobactam MIC > 64), the calculation was performed using the break point as the MIC. In all of these cases, the calculated T > MIC did prove to be subtherapeutic. When patient cultures only grew normal flora, the MIC was estimated as the median MIC for isolates from the 8 study patients who grew *P aeruginosa* (ceftazidime MIC 2 and meropenem MIC 4). The MICs for MSSA against β-lactams were estimated from the literature (ceftazidime MIC 8 and meropenem MIC 0.12).[27,28]

For patients who grew MRSA in their culture, they were evaluated for receipt of MRSA-directed therapy. Of the 5 participants who grew MRSA, 2 regimens did not include MRSA-directed therapy. However, both of these patients were already categorized as subtherapeutic based on β-lactam PD.

Overall, 79% of study participants also received an aminoglycoside that had been adjusted to goal peak concentrations per our institutional guideline. Thus, aminoglycoside use was not used to further divide the participants into therapeutic versus subtherapeutic exposure. Ultimately, 45% (n = 13) of the antibiotic treatment regimens achieved optimal PD indices with at least 1 β-lactam antibiotic and had appropriate MRSA coverage and were considered therapeutic, whereas 55% (n = 16) did not.

After the groups had been established, aminoglycoside use was compared to ensure it would not influence our subsequent analysis. A total of 77% of the therapeutic antibiotic courses included aminoglycosides (IV tobramycin n = 9, and inhaled tobramycin n = 1), and 82% of subtherapeutic antibiotic courses included aminoglycosides (IV amikacin n = 4, and IV tobramycin n = 9). There was also no significant difference in steroid use between the 2 groups, which could further influence improvement in pulmonary function.

Table 2. Pharmacokinetic and Pharmacodynamic Parameters for Antipseudomonal β-Lactam Antibiotics*

	Therapeutic (n = 13)	Subtherapeutic (n = 16)
Calculated antibiotic plasma mid-interval concentrations, mg/L, mean ± SD (n)		
Ceftazidime	12.3 ± 5.8 (11)	5.3 ± 3.6 (7)
Meropenem	1.0 ± 0.9 (3)	0.47 ± 0.34 (10)
Piperacillin	20.3 ± 0 (1)	3.1 ± 3.9 (4)
Imipenem	NA	1.1 ± 0 (1)
Aztreonam	19.2 ± 0 (1)	NA
Highest antibiotic MIC per treatment course, Gram-negative pathogens, mg/L, median ± IQR (n)†		
Ceftazidime	4 ± 1, 8 (3)	>16 ± >16, >16 (7)
Meropenem	6 ± 4, >8 (2)	4 ± 4, 8 (8)
Piperacillin	NA	32 ± 16, >64 (4)
Imipenem	NA	4 (1)
Aztreonam	8 (1)	NA
Antibiotic T > MIC, %, mean ± SD (n)‡		
Ceftazidime	80.4 ± 12.2 (11)	31.4 ± 11.5 (7)
Meropenem	41 ± 12.7 (3)	22.5 ± 4.7 (10)
Piperacillin-tazobactam	51 (1)	25 ± 11.4 (4)
Imipenem	NA	30 (1)
Aztreonam	70 (1)	NA

NA, not available; T > MIC, time above the minimum inhibitory concentration

* To be classified as therapeutic, only 1 β-lactam had to be therapeutic if the participant received more than 1 as part of the treatment course.

† Not all participants grew gram-negative pathogens on culture.

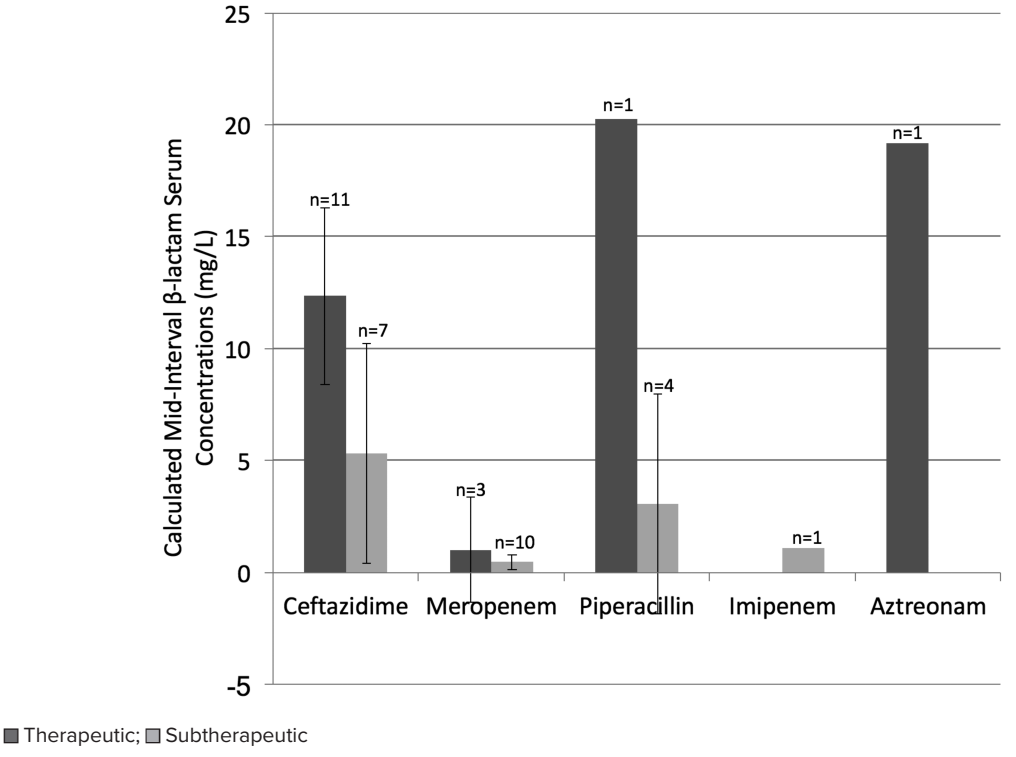
‡ See text for description of determination of T > MIC.

Infecting pathogens, the use of piperacillin-tazobactam, and creatinine clearance (172.9 [SD 12.1] versus 167.2 [SD 12.9] mL/min/1.73 m^2, p = 0.926) did not vary by antibiotic therapy group (Table 3). Although significance was not reached, the following trends were seen: antibiotic days were fewer (14.5 [SD 2.02] versus 18.8 [SD 1.65] days, p = 0.290) and serum creatinine was higher (0.55 [SD 0.06] versus 0.46 [SD 0.05] mg/L, p = 0.076) in the therapeutic group. The use of ceftazidime was associated with therapeutic antibiotic exposure (RR 7.07, 95% CI 1.17–42.85), and the use of meropenem was associated with subtherapeutic antibiotic exposure (RR 0.18, 95% CI 0.03–0.93).

Impact of CF Recommended Dosing on Achievement of Therapeutic PD Indices. The use of US Food and Drug Administration (FDA) versus CFF or European consensus approved dosing guidelines (CF dosing) for antipseudomonal β-lactam antibiotics (n = 38) and whether they achieved therapeutic PD indices are shown in Table 4.[18–20] For 3 commonly used β-lactam antibiotics, the CF dosing guidelines are much larger than the FDA recommendations. The CF dosing for ceftazidime is 300 mg/kg/day (pediatric) or 3 to 4 g every 6 to 8 hours (adult), whereas FDA dosing guidelines recommend 150 mg/kg/day (pediatric) or 2 g every 8 hours (adult).[18–20] The CF dosing for piperacillin-tazobactam is 400 mg/kg/day (pediatric) or 4 g every 6 to 8 hours (adult); FDA dosing recommendations are only 240 to 300 mg/kg/day (pediatric) or 3 to 4 g every 6 hours (adult).[18–20] The CF dosing for aztreonam is 150 mg/kg/day (pediatric) or 2 g every 6 hours (adult), whereas FDA dosing recommendations are only 90 to 120 mg/kg/day (pediatric) or 2 g every 6 to 8 hours (adult).[18–20] Two commonly used β-lactams have similar recommendations for CF dosing and FDA-approved recommendations. The CF dosing for meropenem is 60 to 120 mg/kg/day (pediatric) or 2 g every 8 hours (adult), which is very similar to the FDA dosing recommendations of 60 to 100 mg/kg/day (pediatric) or 2 g every 8 hours (adult).[18–20] The CF dosing for imipenem-cilastatin is 100 mg/kg/day (pediatric) or 1 g every 6 to 8 hours (adult); FDA dosing recommendations are similar at 60 to 100 mg/kg/day (pediatric) or 1 g every 6 hours (adult).[18–20]

The dosing choices selected by the providers reflect this conflict between CF-recommended and FDA-recommended dosing guidelines. However, ceftazidime had therapeutic PD indices 61% of the time (n = 11), even when using the lower FDA dosing guidelines. Meropenem only achieved therapeutic PD indices 23% of the time (n = 3), despite always using the larger CF dosing guidelines. This suggests that the MICs of the bacteria

Figure 2. Calculated midinterval β-lactam serum concentrations. The mean calculated serum concentration for each β-lactam antibiotic is shown. Error bars represent the 95% CI of the mean.



play a crucial role in this determination.

Spirometry Results. Spirometry was performed in each encounter for children ages ≥5 years. Encounter 1 FEV_1 % predicted was used to determine the stage and aggressiveness of the study participant's disease (Figure 1).[23] At baseline, FEV_1 and FVC % predicted were lower in the subtherapeutic group (respectively: 65.1 ± 22.4 versus 95.1 ± 17.3, p = 0.022; and 74.2 ± 17.0 versus 98.3 ± 17.1, p = 0.010). The changes in spirometry values between encounters were compared to explore the relationship between antibiotic exposure and recovery of pulmonary function (Figure 3). Significant differences were found between the therapeutic and subtherapeutic groups for FEV_1 % predicted, FVC, and FEV_1/FVC between encounters 2 and 4. In all cases, those in the subtherapeutic group experienced less of a change than those in the therapeutic group, meaning their improvement in pulmonary function from onset of pulmonary exacerbation to follow-up was less. Significant differences were also found in FEV_1/FVC from encounters 1 to 3 and in $FEF_{25–75}$ % predicted from encounters 2 to 3 and encounters 3 to 4. For FEV_1/FVC 1 to 3, those in the therapeutic group on average had end of antibiotic therapy ratios higher than their baseline, whereas those in the subtherapeutic group were still below their baseline. For $FEF_{25–75}$ % predicted, those in the therapeutic group had significantly more improvement at the end of their antibiotic treatment compared with the onset of the exacerbation. Although both groups had a decrease at follow-up compared with the end of antibiotic therapy, there was less change in the subtherapeutic group.

Discussion

This study investigated the therapeutic use of β-lactam antibiotics among a pediatric population with CF according to PK/PD principles. Unlike aminoglycosides and vancomycin, β-lactam serum antibiotic concentrations are not routinely measured and PK are not established in CF persons during treatment of exacerbations. Ultimately 55% of antibiotic courses for pulmonary exacerbations were subtherapeutic based on the MIC data of the cultured pathogen and a population-based PK modeling for β-lactam drug dosages. In addition, therapeutic PD indices were more often achieved with ceftazidime and less often with meropenem. This finding supports the current therapeutic approach, where ceftazidime and tobramycin in combination is regarded as first-line treatment.[19,29,30] Ceftazidime is prescribed in 44% of all intravenous exacerbation treatments in CFF-accredited care centers, making it the most commonly used antipseudomonal β-lactam within the United States.[7,20] However, other studies have

Table 3. Comparing Infecting Pathogens and Antibiotic Use Between Therapeutic Versus Subtherapeutic Antibiotic Course per Pulmonary Exacerbation

	Therapeutic (n = 13)	Subtherapeutic (n = 16)	Risk Ratio (95% CI)*
Infecting pathogen, n (%)			
Pseudomonas aeruginosa	3 (23)	5 (31)	0.66 (0.12–3.50)
Staphylococcus aureus	5 (38)	6 (37.5)	1.04 (0.23–4.70)
Other pathogens†	3 (23)	9 (56)	0.23 (0.05–1.18)
Normal flora	5 (38)	2 (12.5)	4.38 (0.68–27.98)
β-Lactam antibiotics, n (%)			
Ceftazidime	11 (85)	7 (44)	7.07 (1.17–42.85)
Meropenem	3 (23)	10 (62.5)	0.18 (0.03–0.93)
Piperacillin-tazobactam, n (%)	1 (8)	4 (25)	0.25 (0.02–2.58)
Aminoglycoside, n (%)	10 (77)	13 (81)	0.70 (0.10–4.86)
Steroid, n (%)	8 (62)	10 (62.5)	0.96 (0.20–4.59)

* Using generalized estimating equations to determine the risk ratio (95% CI).
† Other pathogens include: *Escherichia coli*, *Alcaligenes xylosoxidans*, unidentified Gram-negative rod, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and *Haemophilus influenzae*.

shown meropenem/tobramycin combinations to be just as effective as ceftazidime/tobramycin.[30,31]

In our study, this inconsistency appears to be related to a combination of the serum concentrations achieved and the MICs of the bacteria being targeted for treatment rather than the use of CF-approved dosing guidelines. As a result, optimizing dosing based on consensus guidelines may not be sufficient to achieve the best clinical outcomes. Instead, knowing and using the MIC data is critical to get the best results.

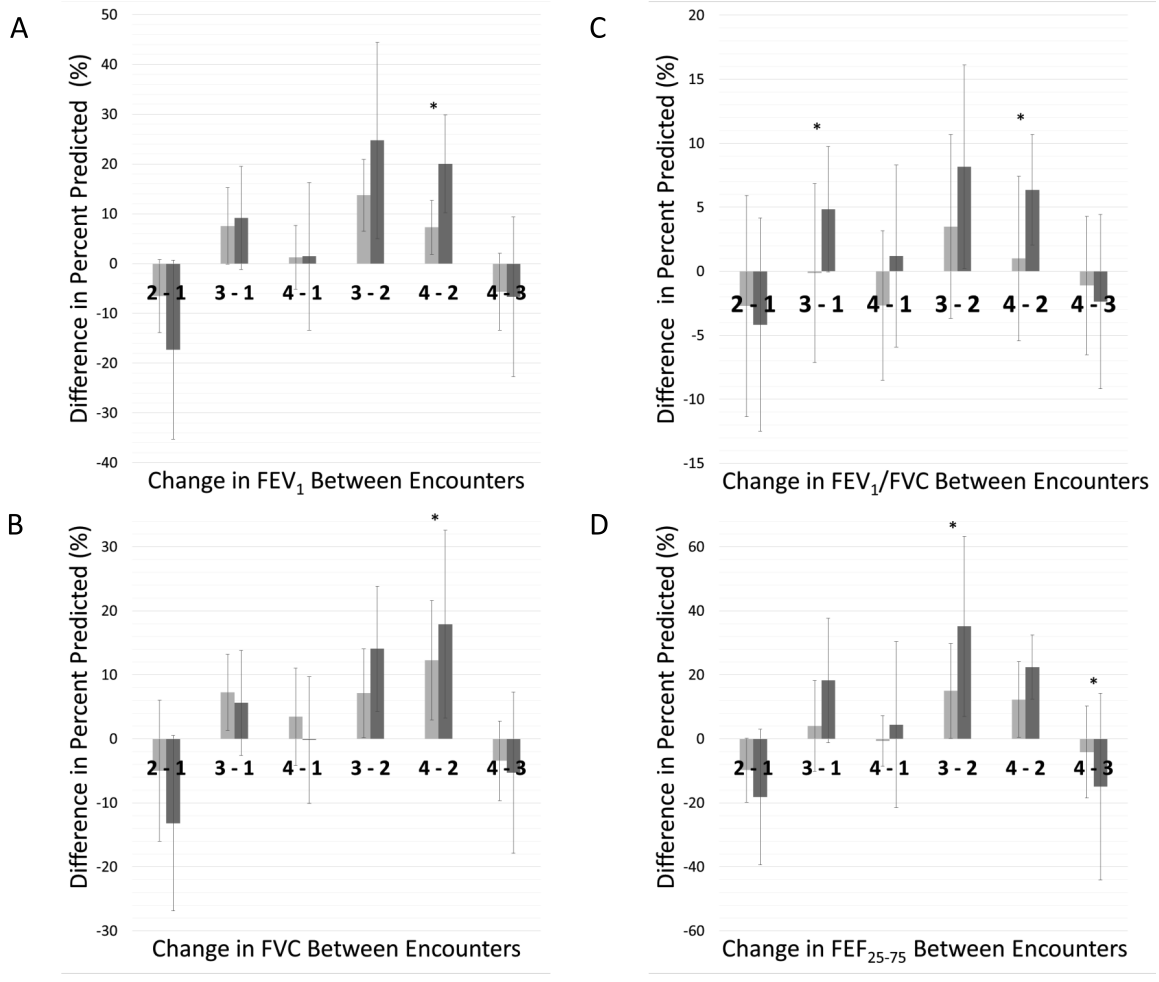
Recent research on the optimization of antipseudomonal antibiotics for pulmonary exacerbations in CF persons has demonstrated that the vast majority of institutions are suboptimally dosing both cephalosporins and carbapenems,[15] and our data support this. Furthermore, CF persons have been shown to have increased renal clearance of β-lactams compared with healthy individuals.[9,10,16] These disease-specific and individual-specific PK variations make it difficult for clinicians to be confident in exposure based on dosing alone. Therapeutic drug monitoring would provide more guidance to physicians in their dosing choices and would likely lead to increased therapeutic β-lactam dosing during CF pulmonary exacerbations. Because of the instability of β-lactams at room temperature, a non-research assay may be difficult to develop. However, the use of population PK models that incorporate patient age, sex, and serum creatinine may serve as a suitable surrogate to ensure the chosen dosing regimen is sufficient to generate serum concentrations above the MIC for the needed amount of time. This additional information could allow for some β-lactam antibiotics (e.g., ceftazidime in this study) to be dosed at the lower FDA-recommended doses to minimize side effects while still achieving optimal PD indices. Likewise, for other β-lactam antibiotics (e.g., meropenem in this study) larger doses or alternative dosing schedules (such as using extended or continuous infusion) may be

Table 4. Antipseudomonal β-Lactam Antibiotic Dosing per Antibiotic Used (N = 38) and Achievement of Therapeutic Pharmacodynamic Indices

	Therapeutic, n (%) (n = 17)		Subtherapeutic, n (%) (n = 21)	
	CF Dosing*	FDA Dosing	CF Dosing*	FDA Dosing
Ceftazidime (n = 18)	0 (—)	11 (61)	0 (—)	7 (39)
Meropenem (n = 13)	3 (23)	0 (—)	10 (77)	0 (—)
Piperacillin-tazobactam (n = 5)	1 (20)	0 (—)	3 (60)	1 (20)
Aztreonam (n = 1)	1 (100)	0 (—)	0 (—)	0 (—)
Imipenem-cilastatin (n = 1)	0 (—)	0 (—)	0 (—)	1 (100)

CF, cystic fibrosis; FDA, US Food and Drug Administration
* CF dosing includes dosing recommendations from the CF Foundation and European consensus guidelines.

Figure 3. Modeling the impact of therapeutic versus subtherapeutic treatments on spirometry values for all exacerbations. The differences in percentage values between encounters 2 and 1 are labeled as 2-1, encounters 3 and 1 are labeled 3-1, etc. (A) Difference in FEV_1 % predicted. (B) Difference in FVC % predicted. (C) Difference in FEV_1/FVC. (D) Difference in $FEF_{25–75}$ % predicted. Shaded bars represent the mean difference in percentage, whereas error bars represent ±1 SD. *p < 0.05. *$FEF_{25–75}$, forced expiratory flow at 25% to 75%; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.*



needed to attain the best clinical outcomes.

In our study, participants who achieved therapeutic β-lactam PD indices were more likely to experience an improvement of their FEV_1 % predicted, FVC, FEV_1/FVC, and $FEF_{25–75}$ % predicted compared with those achieving subtherapeutic PD indices. Of all these results, the most intriguing findings are that the subtherapeutic group had less improvement at follow-up of their FEV_1 % predicted and less improvement of their $FEF_{25–75}$ % predicted at the end of the antibiotic treatment course.

Although we would like to conclude that this difference was due to antibiotics alone, it is important to note that those in the subtherapeutic group had significantly lower FEV_1 % predicted and FVC at baseline compared with the therapeutic group. At baseline, spirometry already suggested respiratory obstruction, with a decreased average FEV_1 % predicted of 65% in the subtherapeutic group, whereas the average FEV_1 % predicted was 90% in the therapeutic group. Although the lower limit of normal is age dependent, normal pediatric values are often 90% or above.[32] This might suggest that those in the subtherapeutic group had less ability to improve from an exacerbation than those in the therapeutic group. Although the change

in FEV_1% predicted may have been influenced by the subtherapeutic group having lower FEV_1% predicted at baseline, there was no significant baseline difference in $FEF_{25–75}$% predicted.

Limitations of this study include the broad inclusion criteria, because young, non–sputum producing patients with mild disease were also compared to older persons with more advanced disease. Another limitation was the use of MIC break points as reported by the lab, because this limited our ability to look more precisely at T > MIC. However, because all of our participants had subtherapeutic T > MIC using the break point MIC (e.g., using MIC 16 when MIC >16 was reported), it did not influence our study outcomes. Furthermore, it is likely that one driver behind achieving therapeutic antibiotic exposure was the bacteria's antibiotic susceptibility as opposed to actual differences in PK (as demonstrated in the case of meropenem). Because study participants had been exposed to antibiotics previously, their higher MICs are likely related to prior antibiotic exposure. As such, study participants with more advanced disease stage tended to be subtherapeutic, and the underlying disease stage of the patient may further impact the ability to recover pulmonary function after antibiotic treatment. This potential combination of both high MIC and low pulmonary function may play an important role in the findings of this study. Lastly, this study does not specifically address either the variability of MICs reported within different subcolonies of *P aeruginosa,* or regional variability.[33,34]

In conclusion, achieving therapeutic β-lactam PD indices was associated with improved clinical outcomes in our cohort of CF persons treated with IV β-lactam antibiotics for pulmonary exacerbations. More interestingly, it was impossible to predict, solely from the dosing regimen used, which patients were going to reach therapeutic serum concentrations. These findings suggest that CF persons may benefit from closer monitoring of their β-lactam exposure and bacterial MIC. One way to monitor would be to perform population PK modeling to determine T > MIC, ideally with serum concentrations available to individualize PK curves. Further research is needed to determine whether real-time therapeutic drug monitoring and/or PK modeling to improve antibiotic exposure, especially when trying to treat antibiotic-resistant organisms, would be beneficial for CF persons in clinical practice.

ARTICLE INFORMATION

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