Pharmacokinetics of Continuous Infusion Beta-lactams in the Treatment of Acute Pulmonary Exacerbations in Adult Patients With Cystic Fibrosis

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BACKGROUND: Several clinical trials have shown the efficacy of continuous infusion beta-lactam (BL) antibiotics in patients with cystic fibrosis (CF); however, little is known about pharmacokinetic changes during the treatment of an acute pulmonary exacerbation (APE). Identifying and understanding these changes may assist in optimizing antibiotic dosing during APE treatment.

METHODS: This study was a retrospective cohort study of 162 adult patients with CF admitted to the University of Utah Hospital between January 1, 2008, and May 15, 2014, for treatment of an APE with both a continuous infusion BL and IV tobramycin. We extracted the administered doses of continuous infusion BLs and tobramycin along with serum drug concentrations and calculated medication clearance rates. The primary outcome was change in clearance rates of continuous infusion BLs between day 2 and day 7 of APE treatment.

RESULTS: The BL clearance rate increased 20.7% (95% CI, 11.42 to 32.49; $P < .001$), whereas the tobramycin clearance rate decreased 6.3% (95% CI, -12.29 to -4.45; $P < .001$). The mean percent predicted FEV₁ increased between admission and discharge by 12.2% (95% CI, -13.81 to 10.55; $P < .001$).

CONCLUSIONS: Clinicians should monitor BL levels along with aminoglycoside levels and make dose adjustments to maximize the chance of optimal antibiotic treatment. Continuous infusion BL and tobramycin clearance can change dramatically during the treatment of an APE, which may necessitate significant changes in dosing to achieve optimal antibiotic levels. Clearance rates of these antibiotics may change in opposite directions, requiring specific monitoring of each medication.

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KEY WORDS: antibiotic therapy; cystic fibrosis; pharmacokinetics

ABBREVIATIONS: AMG = aminoglycoside; APE = acute pulmonary exacerbation; BL = beta-lactam; CF = cystic fibrosis; CrCL = creatinine clearance; SCr = serum creatinine; T > MIC = time above minimum inhibitory concentration

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Cystic fibrosis (CF) is an autosomal recessive disease that affects multiple organ systems, including the lungs, due to the development of thick, viscous secretions.¹ Airway secretions allow persistent bacterial infections to develop and lead to progressive decline in lung function punctuated by exacerbations that may require hospitalization for IV antibiotic therapy. Acute pulmonary exacerbations (APEs) are a leading cause of morbidity and mortality in patients with CF.¹⁻⁴ The most common organisms found during an APE are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. *S. aureus* is more common among children, whereas *P. aeruginosa* becomes more predominant in adults.⁵ Chronic bacterial infections and the multiple courses of antibiotics taken by patients with CF increase the risk for development of multidrug-resistant pathogens.⁶ In adult patients with CF, current recommendations are to combine an antipseudomonal beta-lactam (BL) and an aminoglycoside (AMG) for the treatment of an APE to target *P. aeruginosa*.^{1,2,6}

Compared with patients without CF, those with CF have differences in pharmacokinetic variables, including a greater volume of distribution and increased total body clearance for most antibiotics, leading to a shorter elimination half-life and higher dose requirements.⁷⁻⁹

Patients and Methods

Study Setting and Population

The study included patients at least 18 years of age with CF admitted to the University of Utah Hospital for an APE between January 1, 2008, and May 15, 2014, who were treated with an IV AMG in addition to a continuous infusion antipseudomonal BL. The BLs included aztreonam, ceftazidime, meropenem, piperacillin/tazobactam, and ticarcillin/clavulanate. These patients were included if they had both AMG and BL serum levels drawn on day 2 and day 7 of antibiotic therapy. Repeat antibiotic levels are a consistent practice at our institution, with AMG levels specifically timed at 3 and 10 h postdose. For patients with multiple admissions during the study period, data from the most recent admission were used. Pregnant patients and recipients of dual BL therapy or concurrent vancomycin were excluded. The University of Utah Institutional Review Board approved this study (University of Utah Institutional Review Board 0007667) and deemed it exempt from informed consenting procedures.

Data Sources

We reviewed medical records and collected demographic characteristics, CF genotypes, pulmonary function test results, BL and AMG names, antibiotic dosing, serum antibiotic levels with timing relative to the antibiotic dose administration, SCr level, WBC counts, and temperature. Patients had blood drawn every 3 days during hospitalization for laboratory tests unless otherwise clinically indicated. However, for our study purposes, values upon admission were recorded to describe baseline, along with day 2 and day 7 values, given our interest in changes in antibiotic clearance during that time period. Clinical use of standardized templates for

Enhanced clearance rates are seen with both BLs and AMG antibiotics,¹⁰⁻¹³ but BLs exhibit time-dependent properties with bactericidal activity that increases with time above the minimum inhibitory concentration ($T > MIC$).¹⁴ Therefore, administration of BL antibiotics via continuous infusion maximizes the $T > MIC$ and optimizes bactericidal activity.¹⁵ Current guidelines do not recommend continuous infusion BLs²; however, continuous infusion BLs have shown efficacy in small reported series of patients with CF.¹⁶⁻³² Nevertheless, the majority of reports describe few patients with CF and single determinations of clearance.

The present study examined the clearance rates of continuous infusion BL and AMG antibiotics during the 10- to 14-day treatment of an APE in adult patients with CF. We investigated changes in clearance with continued exposure to antibiotics and explored potential associations between serum creatinine (SCr) and creatinine clearance (CrCl) measurements with clearance rates of AMG and continuous infusion antipseudomonal BLs. We hypothesized an inverse relationship between changes in continuous infusion BL and AMG clearance rates as well as a correlation between changes in antibiotic clearance and renal function.

medication progress notes since 2001 facilitated data collection. Progress notes also contained clearly documented, patient-specific pharmacokinetic parameters, including calculated antibiotic clearance rates based on day 2 and day 7 serum levels. Equations used to calculate clearance rates for both AMGs as well as continuous infusion BLs are displayed in Table 1.³³

Outcomes

The primary outcome was change in clearance rates of the continuous infusion BL from day 2 to day 7 of APE treatment. Secondary outcomes included change in tobramycin clearance rates within the same time period and change in percent predicted FEV₁ (FEV₁%) between admission and discharge. Equations from the Third

TABLE 1] Equations for Clearance Calculations

Aminoglycosides	Continuous Infusion Beta-Lactams
$k_e = [\ln(C_1/C_2)]/t$	$CL = R_0/C_{ss}$
$C_{min} = C_{max} \times e^{-k_e t}$	
$V_d = \text{dose}/k_e \times [(1 - e^{-k_e t}) / [C_{max} - (C_{min} \times e^{-k_e t})]]$	
$CL = k_e \times V_d$	

CL = clearance; C_{max} = maximum concentration; C_{min} = minimum concentration; C_{ss} = steady state concentration; k_e = elimination rate; R₀ = rate of infusion; t = time; V_d = volume of distribution. Data from Sawchuk et al.³³

National Health and Nutrition Examination Survey were used to normalize FEV₁ to FEV₁% because these were the values used to make clinical decisions throughout the study period.³⁴

Statistical Analysis

A paired samples *t* test was used to compare day 2 and day 7 BL and tobramycin clearance rates as well as admission and discharge FEV₁%. A one-way analysis of variance was conducted to compare the change in clearance rates for all BLs. Given the inclusion of any AMG dosing strategy, a sensitivity analysis was performed in which those who received multiple daily doses of an AMG antibiotic were excluded. Pearson correlation coefficient was used to evaluate associations between change in SCr or CrCL and change in antibiotic clearance rates from day 2 to day 7.

Results

All eligible patients were included in the study (N = 162) (Table 2). Table 3 summarizes the antibiotics used along with average initial total daily doses for the selected APE per patient during the study period. Of the BLs, meropenem was used most often (45.7%), followed by piperacillin/tazobactam (19.8%), ticarcillin/clavulanate (19.1%), ceftazidime (11.1%), and, finally, aztreonam (4.3%).

Measured serum BL concentrations indicated that the intended target serum level was attained about 65% of the time (e-Fig 1). The mean clearance rate for continuous infusion BLs increased 20.7% from day 2 to day 7 (95% CI, 11.42 to 32.49; *P* < .001) (Fig 1). There was no difference in the change in clearance rates across BL antibiotics (*P* = .499) (Table 4). The mean increase in BL clearance of 22.76 ± 66.19 mL/min resulted in a mean dose increase of 19.91% during APE treatment.

TABLE 2] Baseline Characteristics (N = 162)

Characteristic	Mean ± SD or No. (%)
Age, y	32.29 ± 9.90
Male sex	78 (48.1)
Height, cm	167.54 ± 9.34
Weight, kg	59.65 ± 13.08
Genotype	
Homozygous dF508	66 (40.7)
Heterozygous dF508	45 (27.8)
G551D	9 (5.6)
Unknown	35 (21.6)
Other ^a	7 (4.3)
FEV ₁ %	44.66 ± 21.41
SCr, mg/dL	0.78 ± 0.22
Temperature, °C	37.10 ± 0.53
WBC count, 10 ⁹ /L	11.33 ± 4.37

SCr = serum creatinine.

^aGenotypes not including dF508 or G551D.

Multivariable linear regression of the change in BL clearance was performed as a function of change in tobramycin clearance rates and CrCL adjusting for age, sex, weight, CF genotype (categorized into mutually exclusive genotype groups), and admission number (number of distinct hospitalizations for each patient during the study period). Adjustments were also made for concurrent nephrotoxic agents, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, nonsteroidal anti-inflammatory drugs, sulfamethoxazole/trimethoprim, rifampin, and contrast media. All model covariates were chosen a priori based on potential confounding factors. There was no evidence of heteroscedasticity, multicollinearity, or other deviations from linear regression assumptions.

Serum levels and dose adjustments for each BL are provided in e-Table 1. BL dosing was increased in 81 patients (50%), maintained in 73 patients (45.1%), and decreased in 8 patients (4.9%) (e-Fig 2). More patients who received piperacillin/tazobactam had a dose increase (84.38%) compared with those who received other BLs. Unlike other BL groups, these dose increases led to an increase in serum levels above goal, rather than within goal.

Tobramycin clearance rates decreased 6.3% from day 2 to day 7 (95% CI, -12.49 to -4.45; *P* < .001 (Fig 1). The mean decrease in tobramycin clearance of -7.97 ± 25.28 mL/min lead to a mean dose reduction of 5.36%. Tobramycin dosing was decreased in 83 patients (51.2%), maintained in 37 patients (22.8%), and increased in 42 patients (25.9%). Nineteen patients (11.9%) admitted prior to 2010 received tobramycin dosed every 8 to 12 h. A sensitivity analysis excluding patients dosed more than once daily found a mean change in tobramycin clearance of -6.22 mL/min (*P* = .004), which was similar in magnitude and statistical significance compared with the original result. Three patients (1.9%) received amikacin rather than tobramycin and had a median reduction in amikacin clearance of 23.8 mL/min (25% decrease) leading to a median dose reduction of 12.1%. Serum AMG levels and

TABLE 3] Antibiotic Usage

Antibiotic	No.	Initial Total Daily Dose (Mean ± SD)
Aztreonam	7	5.71 ± 0.49 g
Ceftazidime	18	5.33 ± 1.28 g
Meropenem	74	5.33 ± 1.74 g
Piperacillin/tazobactam	32	24.82 ± 7.10 g
Ticarcillin/clavulanate	31	23.30 ± 6.45 g
Tobramycin	159	0.56 ± 0.11 g
Amikacin	3	1.58 ± 0.13 g

	Day 2	Day 7	Change	% Change	P value
SCr (mg/dL)	0.78 ± 0.22	0.82 ± 0.24	0.05 ± 0.02	6.66 ± 19.98	.003
CrCl (mL/min)	116.80 ± 36.80	111.86 ± 35.83	-4.94 ± 20.38	-2.57 ± 0.20	.002

Figure 1 – Changes in antibiotic clearance rates (mean ± SD) between day 2 and day 7 of therapy. A statistically significant increase in BL clearance rates occurred ($P < .001$) while AMG clearance rates decreased ($P < .001$) despite an increase in mean SCr and a decrease in mean CrCl. AMG = aminoglycoside; BL = beta-lactam; CrCl = creatinine clearance; SCr = serum creatinine.

subsequent dose adjustments are summarized in e-Table 2 and e-Figure 3, respectively.

FEV₁ increased from a mean of $44.66 \pm 21.41\%$ predicted on admission to $56.84 \pm 25.13\%$ predicted at discharge ($P < .001$), with 36 patients (22.2%) achieving their FEV₁% goal (defined as achievement of the patient's highest FEV₁% within the past year). Although the remainder of patients did not meet their FEV₁% goal, only 10 (6.2%) had a decrease in FEV₁% between admission and discharge. Of note, six of these patients did not achieve target antibiotic levels.

The change in BL clearance between day 2 and day 7 was evaluated, controlling for several variables identified as possible confounders (Fig 2). Thirty-seven patients (22.8%) received concurrent nephrotoxic agents (sulfamethoxazole/trimethoprim

or rifampin) during the treatment period, which seemed to have no significant impact on the change in BL clearance ($P = .398$ and $P = .096$, respectively). The regression model results revealed a significant impact of “other” genotype (Q493X/1154insT, 1717-1G → A/3659delC, E60X/R1158X, R553X/P574H, Q493X/3849+10kbC → T, N1303K/M470V, and S492F/M470V) on the change in BL clearance ($P = .043$). This finding indicates that mean changes in BL clearance rates are 53.61 mL/min less for those with “other” genotypes compared with patients with homozygous dF508 genotype.

As shown in e-Figure 4, no statistically significant correlation was identified between the change in SCr and the change in antibiotic clearance rates for BL ($r = 0.11$; $P = .143$) or AMG ($r = 0.06$; $P = .435$). Similarly, no correlation seems to exist between the change in

TABLE 4] One-Way ANOVA for Beta-Lactam CL Rates

Antibiotic	Change in CL (mL/min)	% Change in CL	P Value
Aztreonam (n = 7)	9.39 ± 12.08	14.51 ± 19.69	.499
Ceftazidime (n = 18)	12.06 ± 19.18	23.49 ± 38.94	
Meropenem (n = 74)	32.07 ± 80.37	20.16 ± 41.06	
Piperacillin/tazobactam (n = 31)	10.07 ± 76.19	13.34 ± 49.03	
Ticarcillin/clavulanate (n = 31)	22.86 ± 32.59	29.59 ± 43.06	

Data are presented as mean ± SD. See Table 1 for expansion of other abbreviation.

Figure 2 – Multivariable linear regression of factors influencing change in BL clearance rates. The regression model suggests no significant impact of the listed factors on change in BL clearance rates with the exception of “other” genotype ($P = .043$), which may reduce the change in BL clearance seen during the first 7 days of therapy compared with those with homozygous dF508 genotype. Reference genotype group = homozygous dF508. Other genotype = genotypes not including dF508 or G551D. SMX/TMP = sulfamethoxazole/trimethoprim. See Figure 1 legend for expansion of other abbreviations.

CrCL and the change in antibiotic clearance rates ($r = 0.12$, $P = .122$ for BL and $r = -0.09$, $P = .240$ for AMG).

Discussion

These study data showed that BL clearance rates changed during the period of treatment for a CF APE. Mean BL clearance rates increased $> 20\%$ within the first week of treatment, which led to a dose adjustment in about 50% of patients and a mean increase in BL dose by nearly 20%. The dose adjustments made to piperacillin/tazobactam led to more supratherapeutic serum levels and fewer levels achieving goal, which suggests room for improvement in the identification of an optimal dose of this antibiotic. Simultaneously, AMG clearance rates also changed. However, contrary to mean BL clearance rates, mean AMG clearance rates decreased by about 6% during the same time frame and led to a 5% decrease in AMG dose. Monitoring of BL and AMG serum levels and calculation of their corresponding clearance rates are needed to optimize antibiotic dosing.

According to our results, changes in antibiotic clearance rates are unrelated to changes in SCr and CrCL levels. Between day 2 and day 7, mean SCr values increased 0.04 mg/dL, leading to a calculated decrease in mean CrCL level of 4.94 mL/min. AMGs are almost entirely eliminated via glomerular filtration,³⁵ which may explain the small decrease in mean AMG clearance rates. However, BL antibiotics undergo glomerular filtration as

well as tubular secretion.³⁶ We hypothesized that this additional mechanism of drug excretion may contribute to the change in BL clearance rates.

The mean increase of 12.2% predicted in FEV₁ is both statistically and clinically significant and compares favorably with other reports.^{37,38} Finding this improvement in FEV₁% is a promising piece of evidence supporting the use of continuous infusion BL antibiotics during APE treatment. However, we cannot directly compare these results with results from the use of conventionally dosed BLs. Confirmation in a randomized clinical trial is warranted.

The finding for “other” genotypes implies a lower change in BL clearance compared with patients with homozygous dF508 genotype. However, this result must be interpreted with caution given the small sample size. The reason for this finding is unclear as it is the combined effect of individual genotypes in the group, none of which was frequent enough to allow for more detailed analyses. To our knowledge, no literature exists regarding change in continuous infusion BL clearance rates in relation to specific genetic mutations.

Our study has several strengths. First, we used a well-annotated dataset, including patient genotypes. All patients admitted for the treatment of an APE without contraindications to BL and AMG therapy had the requisite BL and AMG levels because obtaining antibiotic levels on day 2 and day 7 of APE treatment is the standard of practice at our institution.

Calculation of antibiotic clearance rates was also standardized with the creation of calculators, along with training for any pharmacist taking care of these study patients with CF on how to use these calculators and adjust antibiotic dosing based on drug levels. In terms of data collection, templates for progress notes on patients with CF allowed for consistent documentation of pharmacokinetic information and efficient data collection.

A limitation to the present study is that we could not include all antipseudomonal BLs because some (eg, imipenem, cefepime) are not routinely used at our institution. Ticarcillin/clavulanate was used in some of the study patients, but it is no longer available.³⁹ Prior to 2010, tobramycin was dosed in every 8- to 12-h intervals; however, sensitivity analyses excluding these patients did not change our results. We are unable to confirm whether there are further changes in antibiotic clearance rates between 7 and 14 days of treatment because levels at the end of therapy have no clinical utility. In addition, we cannot ascertain whether the

change in antibiotic clearance is an inducible process that occurs with each antibiotic exposure. Our analysis looked at the most recent admission during the given study period and included number of admissions during the study period in the regression analysis; the analysis revealed no statistical significance, suggesting no cumulative effects of repeated antibiotic treatments. However, this adjustment does not account for possible effects from admissions prior to the study period.

Conclusions

Increasing BL clearance rates during APE treatment in patients with CF frequently necessitates important dose increases to maximize efficacy. On the contrary, AMG clearance rates decreased, leading to a mean dose reduction to minimize antibiotic toxicity. Changes in BL and AMG clearance rates occur independent of renal function. Obtaining serum drug levels is essential to determining optimal dosing for individual patients because there is no correlation between antibiotic clearance rates and measures of renal function.

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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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