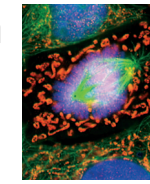
Continuous-Infusion Antipseudomonal Beta-Lactam Therapy in Patients With Cystic Fibrosis



William A. Prescott, Jr., PharmD; Allison E. Gentile, PharmD; Jerod L. Nagel, PharmD; and Rebecca S. Pettit, PharmD, MBA, BCPS

ABSTRACT

Objective: We sought to evaluate the pharmacokinetics, efficacy, safety, stability, pharmacoeconomics, and quality-of-life effects of continuous-infusion antipseudomonal beta-lactam therapy in patients with cystic fibrosis (CF).

Data Sources: Literature retrieval was accessed through MEDLINE (from 1950 to December 2010) using the following terms: cystic fibrosis; beta-lactams or piperacillin or ticarcillin or cefepime or ceftazidime or doripenem or meropenem or imipenem/cilastin or aztreonam; continuous infusion or constant infusion; drug stability; economics, pharmaceutical; and quality of life. In addition, reference citations from identified publications were reviewed.

Study Selection and Data Extraction: We evaluated all articles in English identified from the data sources.

Data Synthesis: Patients with CF often harbor colonies of multidrug-resistant organisms, increasing the risk of suboptimal dosing and failure to meet the time above the minimum inhibitory concentration (T > MIC) pharmacodynamic targets. The pharmacokinetics of continuous-infusion antipseudomonal beta-lactam therapy in CF maintains serum concentrations above the MIC of susceptible strains and is more likely than intermittent infusion to achieve optimal T > MIC targets for some intermediate and resistant strains of *Pseudomonas aeruginosa*.

Three noncomparative and four comparative studies have assessed the efficacy and safety of continuous-infusion antipseudomonal beta-lactam therapy during CF pulmonary exacerbations. Ceftazidime, the most extensively studied antibiotic for continuous infusion in CF, has been shown to improve forced expiratory volume in 1 second (FEV_1), to improve forced vital capacity (FVC), and to extend the time between pulmonary exacerbations. Continuous-infusion cefepime has been studied in a small number of patients, and a trend toward improved pulmonary function has been observed.

Continuous-infusion antipseudomonal beta-lactam therapy appears to be well tolerated, although most of the data pertain to ceftazidime. Because continuous infusion may necessitate that patients wear a portable pump in close proximity to the body, the stability of the antibiotic at body temperature must be considered. Several beta-lactams have good stability at body temperature (piperacillin/tazobactam, ticarcillin/clavulanate, and aztreonam) or acceptable if the medication cartridge is changed twice daily (cefepime and doripenem), whereas other beta-lactams have acceptable 24-hour stability only at lower temperatures (cefepime, ceftazidime, doripenem, and meropenem). Although no pharmacoeconomic studies have evaluated the cost–benefit of continuous infusion versus intermittent infusion in patients with CF, the potential medication cost reduction appears to be considerable. There is little information regarding the impact of continuous infusion on quality of life in patients with CF.

Conclusion: Efficacy and safety studies suggest that ceftazidime, administered as a continuous infusion for the treatment of CF pulmonary exacerbations, is safe and effective; has the potential to reduce the costs of treatment; and is preferred to intermittent infusion among patients treated at home. Continuous-infusion ceftazidime may therefore be an alternative to traditional dosing on a case-by-case basis, such as for patients with multidrug-resistant isolates of *P. aeruginosa*. Treatment with continuous-infusion ceftazidime at home may be considered in such a case, assuming resources and support equivalent to the hospital setting can be ensured. Additional studies assessing the safety and efficacy of other antipseudomonal beta-lactams, when administered as a continuous infusion, during CF pulmonary exacerbations are needed.

Key words: pulmonary, infectious disease, cystic fibrosis, continuous infusion, beta-lactam, monobactam, pulmonary exacerbation, intermittent infusion

INTRODUCTION

Each year, approximately 40% of patients with cystic fibrosis (CF) are admitted to the hospital with a pulmonary exacerbation.[1] Half of these patients are admitted more than once a year, and a quarter of the patients are admitted three or more times each year.[1] Given the 26,500 individuals with CF in the U.S., this extrapolates to more than 18,550 hospitalizations per year.[2]

The management of a CF pulmonary exacerbation consists of intense chest physiotherapy with pharmacotherapy to relieve obstruction and giving antibiotics directed toward the colonizing bacteria to reduce the bacterial burden.[3–5] The Cystic Fibrosis Foundation recommends combination antibiotic therapy during pulmonary exacerbations; this treatment typically consists of an aminoglycoside and an antipseudomonal beta-lactam.[6,7] Patients with CF receive multiple courses of these antibiotics over their lifetime and are therefore more

Dr. Prescott is a Clinical Assistant Professor of Pharmacy Practice at the University at Buffalo School of Pharmacy and Pharmaceutical Sciences, and an Adjunct Instructor at the University at Buffalo School of Medicine, Department of Pediatrics, in Buffalo, N.Y. Dr. Gentile is a Pharmacy Practice Resident at the Women and Children's Hospital of Buffalo in Buffalo. Dr. Nagel is a Clinical Assistant Professor of Infectious Diseases at the University of Michigan Hospitals and Health System in Ann Arbor, Mich. Dr. Pettit is a Pediatric Specialty Resident and an Adjunct Clinical Instructor in the Department of Pharmacy Services and College of Pharmacy at the University of Michigan Hospitals and Health Centers in Ann Arbor.

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likely to acquire and harbor multidrug-resistant bacteria, particularly *Pseudomonas aeruginosa*.[4,5] Because drug manufacturers are not developing new antipseudomonal antibiotics at a rate consistent with the emergence of antibiotic resistance, CF centers and P&T committees must identify alternative methods for delivering currently available antibiotics to optimize treatment.

Beta-lactam antibiotics display time-dependent bactericidal activity. Therefore, their rate of bacterial killing is determined by the length of time the drug concentration exceeds the minimum inhibitory concentration (MIC), which is defined as the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism *in vitro*. Maximal bactericidal activity occurs when the concentration remains above the MIC for 40% to 70% of the dosing interval, depending on the antibiotic, site of infection, and resistance patterns of the infecting pathogen.[8,9]

Antipseudomonal beta-lactams are typically administered by intermittent-infusion dosing (i.e., every 6 to 8 hours over a period of 5 to 30 minutes).[10,11] However, the high rate of beta-lactam elimination in CF in a setting of colonization with multidrug-resistant bacteria increases the risk of failing to optimize the time above the MIC (T > MIC). Considering the prevalence of multidrug-resistant gram-negative bacteria in CF and the lack of new antibiotics that target these bacteria, the use of pharmacodynamic concepts to potentially improve the efficacy of currently available beta-lactams is intriguing. The administration of beta-lactam antibiotics by continuous infusion aims to maximize bactericidal activity by prolonging the T > MIC and is therefore of interest in CF.[12–14]

Although the administration of continuous-infusion antipseudomonal beta-lactams has proved safe and effective in the general population, experience with these regimens in patients with CF is more limited.[10,15–23] At present, the Cystic Fibrosis Foundation does not endorse continuous-infusion beta-lactam therapy during pulmonary exacerbations, citing insufficient evidence supporting its use.[6] However, additional literature has become available since the publication of these guidelines, and survey results from 2010 indicate that approximately 10% of CF centers in the U.S. are now using continuous-infusion or extended-infusion beta-lactam therapy.[10]

In this article, we evaluate the pharmacokinetics, efficacy, safety, stability, pharmacoeconomic, and quality-of-life effects of continuous-infusion antipseudomonal beta-lactam and monobactam therapy in CF. We accessed the literature through MEDLINE (from 1950 to December 2010) using the following terms: cystic fibrosis; beta-lactams or piperacillin or ticarcillin or cefepime or ceftazidime or doripenem or meropenem or imipenem/cilastin or aztreonam; continuous infusion or constant infusion; drug stability; economics, pharmaceutical; and quality of life.

In addition, reference citations from publications identified were reviewed. We evaluated all articles in English identified from the data sources.

PHARMACODYNAMICS

Beta-lactam and monobactam antibiotics exert their bactericidal effects through acetylation of specific cell-wall proteins, thereby altering cell-wall integrity, leading to cell lysis.[8] Maximal antibiotic killing occurs when free unbound antibiotic concentrations exceed the MIC for 50%, 60% to 70%, and 30% to 40% of the dosing interval with penicillins, cephalosporins, and carbapenems, respectively.[18–20] These T > MIC pharmacodynamic targets have been demonstrated *in vitro*, in animal models, and in the treatment of various infections in the general population.[18–20] Optimal T > MIC targets in CF patients have not been established, but goal T > MIC values are similar in published studies and are therefore reasonable targets during CF pulmonary exacerbations.

PHARMACOKINETICS

Several studies have evaluated the pharmacokinetics of ceftazidime (Fortaz, GlaxoSmithKline), cefepime (Maxipime, Elan), piperacillin (Pipracil, Wyeth/Pfizer), meropenem (Merrem, AstraZeneca), and aztreonam (Azactam, Bristol-Myers Squibb) intermittent-infusion and continuous-infusion dosing in CF patients (Table 1).[1,2,15–20,22–36] Pharmacokinetic modeling of ceftazidime intermittent infusion (2 g IV every 8 hours given as a 30-minute infusion) indicates that CF patients achieve a T > MIC of 60% for organisms with an MIC of 1 mg/L or less.[37,38] In comparison, Monte Carlo simulation of ceftazidime 6 g, as given by continuous infusion, has predicted an increased probability of achieving the goal T > MIC for some intermediate or resistant strains of *Pseudomonas*: T > MIC of 65% for 100%, 80%, and 10% of organisms with an MIC of 8, 16, and 32 mg/L, respectively.[37] Similarly, a pharmacokinetic study of cefepime using a 15-mg/kg loading dose, followed by a continuous infusion of 100 mg/kg per day, resulted in a steady-state concentration (C_{ss}) of 28.4 mg/L, providing an optimal T > MIC for all susceptible and some nonsusceptible *Pseudomonas* strains.[23]

Monte Carlo simulation of piperacillin intermittent infusion (3 g IV every 4 hours), administered as a 30-minute infusion, or 18 g/day, indicates an 80% probability of achieving a T > MIC of at least 50% at an MIC of 16 mg/L.[26] By comparison, piperacillin, administered by continuous infusion in a daily dose of 9 g, increases the probability of achieving a T > MIC of at least 50% at an MIC of 16 mg/L to 90%.[26]

In a pharmacokinetic study of meropenem, a loading dose of 100 mg, followed by a continuous infusion of 3 g/day, resulted in a mean C_{ss} of 8.31 mg/L, exceeding the MIC of susceptible *P. aeruginosa* isolates. Increasing the loading dose to 200 mg, paired with a continuous infusion of 6 g/day, resulted in a mean C_{ss} of 18.50 mg/L, exceeding the MIC of susceptible and some nonsusceptible isolates.[36]

Monte Carlo simulation of aztreonam intermittent infusion suggests that 100% of patients receiving 1 g every 8 hours achieve a T > MIC of at least 50% for organisms with an MIC of 1 mg/L or less, whereas 98%, 82%, 24%, and 0% of patients obtain a T > MIC of at least 50% for organisms with an MIC of 2, 4, 8, and 16 mg/L, respectively.[25] Increasing the dosage to 2 g every 8 hours results in 100% of patients obtaining a T > MIC of at least 50% for organisms with an MIC of 2 mg/L or less, whereas 98%, 83%, and 28% of patients obtain a T > MIC of at least 50% for organisms with an MIC of 4, 8, and 16 mg/L, respectively (no patients obtained a T > MIC of at least 50% at an MIC of 32 mg/L). Aztreonam 200 mg/kg per day, given by

Table 1 Pharmacokinetics of Intermittent-Infusion and Continuous-Infusion Antipseudomonal Beta-Lactams In Cystic Fibrosis*

Dosing Regimen	Loading Dose Conc. (Max. Dose)	Dosage (Max. Dose/Day)	Age (Years) (Range)	C_{max} (mg/L)	C_{ss} (mg/L)	Serum T > MIC	Sputum Conc. (mg/L)
Ceftazidime							
II[32]	N/A	50 mg/kg (1 dose)	20.8 (16–25.6)	211.0[a]	N/A	72.1% @ MIC 8[a]	N/R
II[19]	N/A	200 mg/kg/day div q8h	12.6 (5–16.8)	N/R	N/A	N/R	2.2 ± 1.5
II[30]	N/A	200 mg/kg/day div q8h	14.4 (5–37)	159.0 ± 44.0	N/A	100% @ MIC 8[a]	N/R
II[17]	N/A	200 mg/kg/day div q8h	23.3	216.3 ± 71.5	N/A	100% @ MIC 8[a]	N/R
CI[18]	7.5 mg/kg	82 mg/kg/day[b]	N/R (9–25)	N/A	21.3–27.1[c]	100% @ MIC 8	N/R
CI[19]	N/R	100 mg/kg/day	12.6 (5–16.8)	N/A	28.5 ± 8.4	100% @ MIC 8	2.1 ± 1.1[d]
CI[30]	N/R	100 mg/kg/day	14.4 (5–37)	N/A	32.0 ± 12.0	100% @ MIC 8	N/R
CI[20]	15 mg/kg	100 mg/kg/day	26.9 (15–52)	N/A	28.4 ± 5.0	100% @ MIC 8	1.6 ± 1.6
CI[31]	2,000 mg	100 mg/kg/day	25.6 (22–30)	N/A	28.7 ± 5.0	100% @ MIC 8	1.6 ± 1.6
CI[18]	10 mg/kg	108 mg/kg/day[e]	N/R (9–25)	N/A	38.3–39.2[c]	100% @ MIC 8	N/R
CI[15]	65 mg/kg	200 mg/kg/day	19 (10–32)	N/A	56.1 ± 23.3	100% @ MIC 8	1.7 ± 2.2
CI[17]	60 mg/kg (2 g)	200 mg/kg/day (12 g)	23.3	N/A	56.2 ± 23.2	100% @ MIC 8	N/R
CI[29]	100 mg/kg	300 mg/kg/day	N/R[f]	N/A	52.9–63.4[g]	100% @ MIC 8	N/R
Cefepime							
II[34]	N/A	2,000 mg (1 dose)	24.0 (18–31)	156.0 ± 23.2	N/A	100% @ MIC 8[a]	N/R
II[35]	N/A	150 mg/kg/day div q8h	16.2 (8–27)	136.1	N/A	100% @ MIC 8[a]	N/R
II[33]	N/A	150 mg/kg/day div q8h	18.4 (4–41)	141.3 ± 34.9	N/A	44% @ MIC 32 19% @ MIC 64	6.3 ± 5.4
II[23]	N/A	150 mg/kg/day div q8h	N/R[h]	130	N/A	36%–83% @ MIC 4–12	N/R
CI[23]	15 mg/kg	100 mg/kg/day (6 g)	N/R[h]	N/A	28.4[i]	100% @ MIC 8	N/R
Piperacillin							
II[26]	N/A	4,000 mg (1 dose)	21.0 ± 4.0	767	N/A	31% @ MIC 64[a]	N/R
CI[28]	N/R	300 mg/kg/day (16 g)	25.8	N/A	32.8 ± 14.4	0% @ MIC 64	N/R
Meropenem							
II[1]	N/A	6,000 mg/day div q8h	23.6	113.0 ± 13.0	N/A	> 50% @ MIC 4	N/R
II[2]	N/A	15 mg/kg (1 dose)	24.0 ± 4.0	79.4 ± 19.7	N/A	39% @ MIC 4	N/R
CI[36]	100 mg	3,000 mg/day	27.0 ± 10	N/A	8.31 ± 0.68	100% @ MIC 4	N/R
CI[36]	200 mg	6,000 mg/day	27.0 ± 10	N/A	18.50 ± 3.31	100% @ MIC 4	N/R
Aztreonam							
II[24]	N/A	30 mg/kg (1 dose)	14	184.9	N/A	74% @ MIC 8[a]	N/R
II[25]	N/A	3,000 mg/day div q8h	29.8 ± 3.2	28	N/A	N/R	N/R
CI[16]	N/R	200 mg/kg/day	0.25[j]	N/A	160	100% @ MIC 4	N/R

* All values are reported as mean ± standard deviation (range) unless otherwise indicated.

CI = continuous infusion; C_{max} = maximum serum concentration; Conc. = concentration; C_{ss} = steady-state concentration; div = divided; II = intermittent infusion; Max. = maximum; N/A = not applicable; N/R = not reported; q8h = every 8 hours; T > MIC = time above the minimum inhibitory concentration.

[a] Derived by authors from available data.

[b] Reported by authors as an approximate dose based on an infusion rate of 3.4 mg/kg per hour.

[c] Levels on day 7 of therapy reported.

[d] Reported as mcg/g.

[e] Reported by authors as an approximate dose based on an infusion rate of 4.5 mg/kg per hour.

[f] Population described by authors as "children."

[g] Concentrations reported as a range of means collected over 8 to 72 hours following initiation of treatment.

[h] Population described by authors as "adult."

[i] Values reported are medians.

[j] Data based on a case report of a single patient.

continuous infusion to an infant with CF, yielded a C_{ss} of 160 mg/L, exceeding the cultured *P. aeruginosa* MIC of 4 mg/L for the entire dosing interval.[16]

The differences in the pharmacokinetics of ceftazidime at the site of infection (i.e., in bronchial fluid), when given by continuous or intermittent infusion, are not well established. Sputum concentrations fall below the MIC of most *Pseudomonas* isolates, with reported concentrations of 1.6 to 2.1 mg/L and 2.2 mg/L for continuous infusion and intermittent infusion, respectively (see Table 1).[15,19,20,31] However, the data are limited by small samples and by inconsistent timing of sputum concentrations, which do not allow definitive conclusions to be made regarding comparative sputum pharmacokinetics for intermittent-infusion and continuous-infusion dosing.

EFFICACY

Three noncomparative studies involving a total of 35 patients and four comparative studies involving 98 patients have assessed the efficacy of continuous-infusion antipseudomonal beta-lactam therapy for CF.[15,17–21,23] Of the four studies that compared intermittent-infusion and continuous-infusion beta-lactam therapy, three investigated the efficacy of continuous-infusion ceftazidime[17,19,21] and one investigated the efficacy of continuous-infusion cefepime (Table 2; see page 735).[23]

Noncomparative studies suggest that continuous-infusion ceftazidime brings about clinical improvement among CF patients receiving treatment for a pulmonary exacerbation.[15,18,20] In a study of six CF patients (9–25 years of age), continuous-infusion ceftazidime, administered via a portable infusion device, resulted in improvements in clinical condition.[18] In another study, all 12 CF patients (10–32 years of age; mean age, 19 years) who received continuous-infusion ceftazidime improved clinically.[15] However, the criteria for clinical improvement were not specified in either study. In a third study, 17 CF patients (15–52 years of age; mean age, 26.9 years) received continuous-infusion ceftazidime via a portable infusion pump for 21 days. Of the treated patients, 84% had an excellent clinical response, based on weight gain, pulmonary examination, pulmonary function tests, and subjective findings. Although a significant ($P < 0.05$) increase in forced expiratory volume in 1 second (FEV_1) was observed, FEV_1 returned to baseline at follow-up 4 to 6 weeks later.[20]

In a small nonrandomized, prospective, crossover study, five adults (19–32 years of age), hospitalized for a pulmonary exacerbation, were treated with ceftazidime, given by either intermittent or continuous infusion via a nonportable programmable infusion pump (see Table 2).[21] During the initial hospitalization, ceftazidime was administered via intermittent infusion. During the second hospitalization, ceftazidime was administered via continuous infusion to achieve a serum concentration of 6.6 times the MIC of the most resistant strain of *P. aeruginosa* (mean dosage, 78 mg/kg per day). Infusions were interrupted for a maximum of 3 hours per day to administer other intravenous (IV) medications. All patients were treated concomitantly with parenteral and inhaled aminoglycosides. The investigators attempted to keep respiratory therapy and concomitant medications constant during both hospital admissions. Pulmonary function tests, including FEV_1, forced vital capacity (FVC), and bacterial density in sputum, were measured on days 1, 4, and 10 as well as 2 weeks after the completion of therapy. The white blood cell (WBC) count was measured on days 1, 4, and 10.[21]

Pulmonary function test results improved during each treatment, but no statistically significant differences in FEV_1 or FVC were observed between the regimens at the end of treatment or on follow-up 2 weeks later (see Table 2). Decreases from baseline in bacterial density in sputum and in the WBC count were observed; again, the differences between regimens were not statistically significant.[21]

In a nonrandomized, prospective crossover study, 14 pediatric CF patients (5–17 years of age) with moderate lung disease (mean baseline FEV_1, 52.1%–54.6% predicted value) who were hospitalized for a pulmonary exacerbation received ceftazidime, administered either as an intermittent infusion or as a continuous infusion by means of a portable infusion pump (see Table 2).[19] All patients were treated concomitantly with IV amikacin 20 mg/kg (Amikin, Bristol-Myers Squibb) once daily, although the amikacin goal and measured serum concentrations were not reported. Intensive respiratory physiotherapy and standard medication treatments remained unchanged throughout the study. Outcome measures, including FEV_1, FVC, inflammatory markers, and nutritional status indices, were obtained on days 1 and 14 of therapy.

An improvement from baseline in all efficacy variables, including FEV_1 and FVC, was reported (see Table 2). The mean FEV_1 and FVC in the intermittent-infusion group increased from 54.6% to 69.9% predicted and from 78.6% to 90.1% predicted, respectively. In comparison, the mean FEV_1 and FVC in the continuous-infusion group increased from 52.1% to 70.6% predicted and from 70.5% to 85.6% predicted, respectively. However, no statistically significant difference in FEV_1 or FVC was observed between the regimens. Except for prealbumin, no statistically significant difference in inflammatory or nutritional markers was noted.[19]

Huibert and colleagues conducted a randomized, multicenter crossover study of 69 patients (older than 8 years of age) with moderate lung disease (mean baseline FEV_1, 42.6% to 45.8% predicted) to compare intermittent-infusion and continuous-infusion ceftazidime for the treatment of pulmonary exacerbations (see Table 2).[17] During intermittent infusion, ceftazidime was administered in three divided doses as a 30-minute infusion. During continuous infusion, ceftazidime was administered via a portable infusion pump over 23 hours. The duration of therapy for each regimen depended on the severity of the pulmonary exacerbation and was similar for each treatment course. All patients were treated concomitantly with once-daily tobramycin 10 mg/kg (Nebcin, Eli Lilly), although tobramycin serum concentrations were not reported. Therapy with oral ciprofloxacin (Cipro, Bayer) was allowed, provided that it was given in an identical manner during both the intermittent-infusion and continuous-infusion treatment courses. Secondary efficacy outcomes included the interval between antibiotic treatment courses and the change in inflammatory indices.[17]

An improvement from baseline in FEV_1, the primary efficacy outcome, was observed with each regimen. The mean FEV_1 in the intermittent-infusion group increased from 44.4% to 50.0% predicted in the per-protocol analysis and from 44.3% to 49.8%

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Table 2 Comparative Efficacy of Continuous-Infusion and Intermittent-Infusion Antipseudomonal Beta-Lactams In Cystic Fibrosis*

Study Design	No. of Patients		Age	Antibiotic	Dosage, mg/kg per day (Max)		Duration (Days)	FEV_1 (% Predicted)		FVC (% Predicted)	
	CI	II			CI	II		CI	II	CI	II
Comparative, crossover[21]	5	5	23.4	Ceftazidime	78[a]	123[b]	10	+0 .17 (0.25)[c,d]	+ 0.29 (0.15)[c,d]	+ 0.27 (0.65)[c,d]	+ 0.52 (0.28)[c,d]
Comparative, crossover[19]	14	14	12.6	Ceftazidime	100[e]	200[f]	14	+ 18.5[d]	+ 15.3[d]	+ 15.1[d]	+ 11.5[d]
Randomized, comparative, crossover[17]	69	69	22.6–24.3	Ceftazidime	200[e,g] (12 g)	200[h] (12 g)	14–21	+ 7.6 (12.1)[d]	+ 5.5 (10.6)[d]	N/R	N/R
Randomized, comparative[23]	5	5	N/R	Cefepime	100[e,i] (6 g)	150[h] (6 g)	14	+ 16.8[d]	+ 9.55[d]	N/R	N/R

* ΔFEV_1 and ΔFVC are reported as change from day 1 to completion of therapy. Values are expressed as mean (standard deviation) unless otherwise indicated.

CI = continuous infusion; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; II = intermittent infusion; Max. = maximum; N/R = not reported.

[a] Mean dose calculated to achieve 6.6 x MIC of the most resistant *Pseudomonas aeruginosa* isolate.

[b] Mean dose based on 150 mg/kg per day divided into three doses (maximum: 6 g/day), administered over unspecified infusion time.

[c] Values reported in liters.

[d] $P > 0.05$ for comparison of mean change between regimens.

[e] Portable infusion pump used for administration.

[f] Administered every 8 hours via 20-minute infusions.

[g] Continuous infusion administered after loading dose of 60 mg/kg (maximum: 2 g).

[h] Administered every 8 hours via 30-minute infusions.

[i] Continuous infusion administered after a loading dose of 15 mg/kg.

predicted in the intention-to-treat (ITT) analyses. By comparison, the mean FEV_1 in the continuous-infusion group increased from 42.8% to 52.4% predicted in the per-protocol analysis and from 42.7% to 50.3% predicted in the ITT analyses.[17]

Although a statistically significant improvement in FEV_1 was observed with continuous infusion in the per-protocol analysis (mean improvement, 9.6% predicted vs. 5.6% predicted; $P = 0.02$), the difference did not reach statistical significance in the ITT analysis (mean improvement, 7.6% predicted vs. 5.5% predicted; $P = 0.15$) (see Table 2). Patients with resistant isolates of *P. aeruginosa* showed significantly greater improvement in FEV_1 with continuous infusion (mean improvement, 6.2% vs. 1.7%; $P < 0.05$). The time between pulmonary exacerbations was significantly longer for patients receiving ceftazidime via continuous infusion (3.2 months) when compared with intermittent infusion (2.8 months; $P = 0.04$).[17]

This is the largest study of continuous-infusion beta-lactam therapy conducted to date. The findings suggest that the improvement in FEV_1 with ceftazidime, when given by continuous infusion, is similar to that of intermittent infusion and that continuous infusion results in a reduction of approximately one CF exacerbation (and potentially one hospital admission) every 2.5 years.

In a small randomized, prospective, comparative study, 10 adults with a pulmonary exacerbation (nine completed the study) received cefepime by either intermittent infusion or continuous infusion via a portable infusion pump (see Table 2).[23] Patients in the continuous-infusion and intermittent-infusion groups had severe CF lung disease (mean FEV_1, 35.5%) and moderate CF lung disease (mean FEV_1, 49%), respectively. All patients received tobramycin, although tobramycin serum concentrations were not reported.

Each regimen resulted in an increase in FEV_1 from baseline (see Table 2). The improvement in FEV_1 appeared to be greater in the continuous-infusion group, but the difference between the regimens was not statistically significant, possibly reflecting the study's small sample size.[23]

Ceftazidime, the most extensively studied antibiotic for continuous infusion in CF, improves FEV_1 and FVC and extends the time between pulmonary exacerbations. Therefore, ceftazidime appears to be a reasonable treatment option, particularly for patients who have not responded to traditional dosing methods or who have multidrug-resistant isolates of *P. aeruginosa*.

Continuous-infusion cefepime has been studied in a small number of patients with CF, and although the results suggest improved pulmonary function, additional research is needed. Further studies of the efficacy of continuous-infusion piperacillin, doripenem (Doribax, Janssen), imipenem/cilastatin (Primaxin, Merck), meropenem, and aztreonam in the treatment of CF are also needed to determine the non-inferiority of these antibiotics before their routine use can be recommended.

SAFETY

Continuous infusion of ceftazidime for up to 21 days has been well tolerated in both children and adults with CF.[15,17,19,20,31] The most frequently reported adverse events (AEs) (with a similar frequency for continuous and intermittent infusions)

include a transient increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, abdominal pain, nausea, diarrhea, hemoptysis, headaches, pulmonary exacerbations, and tonsillitis.[17]

Of note, ceftazidime contains a pyridinium moiety in its C3 side chain, which on degradation results in the release of pyridine, a chemical that has been associated with renal and hepatic toxicities.[39,40] The U.S. Pharmacopeia has determined the upper limit of pyridine in ceftazidime for IV infusion to be 1.1 mg/mL.[39] At 37° C, the pyridine concentration in ceftazidime 12% weight/volume exceeds the limit of 1.1 mg/mL after 8 hours, increasing from less than 0.1 mg/mL at baseline to more than 4 mg/mL at 24 hours.[39] This may be important when continuous-infusion dosing is used, because ceftazidime may be exposed to higher temperatures or infused over periods exceeding 8 hours.

In a retrospective study conducted to correlate pyridine to hepatic toxicity in 109 patients with CF receiving multiple courses of antibiotics over 5 years, the investigators found an increase in AST and ALT. However, a definitive relationship between pyridine accumulation and the observed increase in AST and ALT could not be established.[40]

In a small crossover study of seven adults with CF (mean age, 27 years), meropenem was reportedly well tolerated when administered as a continuous infusion via a portable infusion pump for 24 hours.[36] A continuous infusion of aztreonam for 14 days was tolerated without AEs in a 3-month-old infant with CF.[16]

Overall, several small studies suggest that continuous infusion of antipseudomonal beta-lactam antibiotics is well tolerated, although most of the data pertain to ceftazidime. When ceftazidime is given via continuous infusion, the drug's stability must be considered, as this may affect the safety profile.

Safety data are limited for continuous-infusion meropenem and aztreonam, and such data are not available for continuous-infusion cefepime, piperacillin, doripenem, or imipenem/cilastatin. However, these agents are often used as intermittent infusion for the treatment of CF pulmonary exacerbations without producing significant toxicity.

DRUG STABILITY

The stability of an antibiotic depends on several factors: the drug's concentration, the IV solution in which the drug is delivered, the storage temperature, and the infusion device used.[41] Further, if continuous-infusion beta-lactam therapy is administered over 24 hours without interruption, Y-site compatibility with concomitant IV medications, such as the aminoglycosides, must be considered.

Although the drug concentration and the IV solution can be standardized and Y-site compatibility can be accounted for, the storage temperature is more difficult to control, particularly when treatment is completed in the outpatient environment. The storage temperature depends on the geographic location and season, and the stability of the antibiotic may therefore vary from region to region and from month to month. Moreover, in published studies, the portable pump was often worn under clothing, in close proximity to the body, thereby exposing the antibiotic to temperatures that may have approximated the body's temperature (around 37° C). Therefore, the stability of the antibiotic at this temperature must be considered when continuous-infusion beta-lactam therapy is administered in this manner.

If antibiotic loss exceeds 10% during the 24-hour continuous infusion, which is the limit set by the U.S. Pharmacopeia for most beta-lactams,[42] the potential impact on serum concentrations must be considered. Many studies assessing the efficacy of continuous-infusion beta-lactams in CF have been conducted in this setting, with a portable infusion pump used to administer the antibiotic over 23 to 24 hours.[17,19,20,23,31,36]

Ceftazidime and cefepime have good stability at room temperature, but 90% stability is maintained for only a limited period when these drugs are stored at body temperature (Table 3).[39,43] Of additional concern, color changes have been observed when cefepime is stored at temperatures exceeding 30° C; the clinical implication of this observation is still unclear.[39,41] The significant degradation of both ceftazidime and cefepime that occurs at temperatures exceeding 25° C may limit the usefulness of these antibiotics when they are delivered via portable infusion pumps stored near the body, although the efficacy of ceftazidime does not appear to have been compromised in published research.[17] These agents do show improved stability at lower temperatures, and ceftazidime has been administered by continuous infusion to healthy adults via a portable pump stored in a cold pouch.[44]

Piperacillin, ticarcillin (Ticar, GlaxoSmithKline), and aztreonam have acceptable stability for administration via continuous infusion. At temperatures close to body temperature (35°–37° C), piperacillin, piperacillin/tazobactam (Zosyn, Wyeth/Pfizer), ticarcillin/clavulanate (Timentin, GlaxoSmithKline), and aztreonam all maintain stability for adequate periods (see Table 3).[39,41] The beta-lactamase inhibitors tazobactam and clavulanate maintain ≥ 98% stability over the same periods.[41] Color changes have been observed with ticarcillin/clavulanate, but not with piperacillin or aztreonam, when stored at temperatures of 35° C.[41] As with cefepime, the clinical importance of these color changes remains to be determined.

Carbapenems appear to be the most unstable of the antipseudomonal beta-lactams for continuous infusion (see Table 3).[39,45,46] At body temperature, imipenem/cilastatin exhibits 60% degradation over 24 hours.[39] Similarly, meropenem exhibits 55% to 70% degradation over 24 hours at body temperature, although this degradation is concentration-dependent.[39,47] However, when the storage temperature of meropenem is maintained at 4° C, 90% stability can be retained for up to 24 hours (see Table 3).[39] In one study, when meropenem was administered via a portable infusion pump stored in a cold pouch, the drug maintained 90% stability or higher for 12 to 16 hours in 4/4 pumps and for up to 24 hours in 3/4 pumps (the pump with less than 90% stability contained 86.3% of the initial concentration).[36]

Doripenem is stable for 24 hours at room temperature (25° C) when diluted in normal saline and in sterile water for injection, and it is stable for 12 hours at body temperature when diluted in sterile water for injection.[46,47] When the temperature is maintained at 4° C, doripenem can remain stable for 10 days when it is diluted in normal saline (see Table 3).[46] Doripenem therefore appears to be slightly more stable than either imipenem/cilastin or meropenem.

Ceftazidime, imipenem/cilastin, and meropenem are relatively unstable when stored at body temperature. Drug degradation during continuous infusion, given via a portable infusion pump, may lead to lower serum concentrations, potentially compromising efficacy. Storing the infusion pump in a cold pack to maintain lower temperatures with the goal of improving stability (with ceftazidime and meropenem) or renewing the contents of the infusion pump more frequently than every 24 hours (i.e., every 8 hours with ceftazidime) should be considered if these antibiotics are administered via continuous infusion by means of a portable infusion pump.[36,43,44] However, the efficacy and safety of continuous-infusion beta-lactam treatment with alterations in storage conditions have not been well studied.

Cefepime and doripenem are stable for approximately 12 hours at body temperature and therefore could be used for continuous infusion without a cold pack if the medication cartridge is changed every 12 hours.

Piperacillin/tazobactam, ticarcillin/clavulanate, and aztreonam appear to be the most stable antipseudomonal beta-lactams at body temperature and may thus be administered as continuous infusions without concern for drug degradation. Given the favorable stability profile of these agents, efficacy and safety studies of continuous infusion in CF are warranted.

Table 3 Stability of Antipseudomonal Beta-Lactams When Administered via Continuous Infusion

Antibiotic	Conc. (mg/mL)	Diluent	Stability (Hours)[a]				
			4°C	25°C	30°C	35°C	37°C
Ceftazidime[43]	50–120	SWFI	N/R	> 24	N/R	N/R	N/R
Ceftazidime[39]	120	SWFI	N/R	24	N/R	N/R	8
Cefepime[41]	28	NS	N/R	N/R	N/R	< 24	N/R
Cefepime[39]	50	SWFI	≥ 24	20.5	N/R	N/R	13
Cefepime[43]	50–120	SWFI	N/R	≤ 24	N/R	N/R	≤ 12
Piperacillin[39]	128	SWFI	≥ 24	~ 30	N/R	N/R	21.67
Piperacillin/tazobactam[41]	9	NS	N/R	N/R	N/R	24	N/R
Piperacillin/tazobactam[41]	49.5	NS	N/R	N/R	N/R	24	N/R
Piperacillin/tazobactam[41]	90	NS	N/R	N/R	N/R	< 24	N/R
Piperacillin/tazobactam[39]	128	SWFI	N/R	> 72	N/R	N/R	> 24
Ticarcillin/clavulanate[41]	12	NS	N/R	N/R	N/R	24	N/R
Ticarcillin/clavulanate[41]	70	NS	N/R	N/R	N/R	24	N/R
Ticarcillin/clavulanate[41]	150	NS	N/R	N/R	N/R	24	N/R
Imipenem/cilastatin[45]	5	NS	N/R	N/R	6	4	3[b]
Imipenem/cilastatin[39]	8	SWFI	N/R	3.5	N/R	N/R	2.75
Meropenem[45]	5	NS	N/R	N/R	12	8	6[b]
Meropenem[47]	40	SWFI	N/R	~ 10	N/R	N/R	6
Meropenem[47]	60	SWFI	N/R	6	N/R	N/R	N/R
Meropenem[39]	64	SWFI	≥ 24	5.25	N/R	N/R	1.83
Doripenem[45]	5	NS	N/R	N/R	16	12	8[b]
Doripenem[46]	5	D5W	240	16	N/R	N/R	N/R
Doripenem[46]	5–10	NS	240	24	N/R	N/R	N/R
Doripenem[46]	10	D5W	168	16	N/R	N/R	N/R
Doripenem[47]	10	SWFI	N/R	24	N/R	N/R	12
Aztreonam[41]	1.1	NS	N/R	N/R	N/R	> 72	N/R
Aztreonam[41]	6.2	NS	N/R	N/R	N/R	> 72	N/R
Aztreonam[41]	11.3	NS	N/R	N/R	N/R	> 72	N/R
Aztreonam[39]	100	SWFI	N/R	> 24	N/R	N/R	N/R

Conc. = concentration; D5W = Dextrose 5% in Water; N/R = not reported; NS = Normal Saline (0.9% NaCl); SWFI = Sterile Water for Injection.
[a] Stability based on maintenance of ≥ 90% initial drug concentration.
[b] Stability tested at 40°C.

PHARMACOECONOMICS

Although no published pharmacoeconomic studies have compared the cost–benefit of continuous infusion with intermittent infusion of antipseudomonal beta-lactams in patients with CF, continuous infusion may have a positive effect on the direct costs of care in this patient population.[17,19,21] As noted previously, the period between pulmonary exacerbations was significantly longer for patients who received ceftazidime via continuous infusion (3.2 months) than for those receiving intermittent infusion (2.8 months; $P = 0.04$), which extrapolates to a reduction of approximately one CF exacerbation (and potentially one hospital admission) every 2.5 years.[17]

Compared with intermittent-infusion dosing regimens, continuous-infusion beta-lactam therapy achieves target serum concentrations for susceptible organisms using a 41% to 50% lower total daily dose of ceftazidime and a 17% lower daily dose of cefepime.[19,21,23] The mean average wholesale price (AWP) of ceftazidime is $10.64 per gram (range, $7.25 to $16.18 per gram).[48] Based on a daily dose requirement of 6.00 to 7.75 g with intermittent infusion versus 3.552 to 3.875 g with continuous infusion,[19,21] administering ceftazidime by continuous infusion would reduce the costs associated with this antibiotic by an estimated $364.65 to $577.22 for a 14-day treatment course and by $546.98 to $865.83 for a 21-day treatment course. Based on annual hospitalization rates for CF pulmonary exacerbations, this equates to a total annual reduction in medication costs of approximately $6.8 to $10.7 million (assuming all regimens include a 14-day course of ceftazidime), or approximately $10.1 to $16.1 million (assuming all regimens include a 21-day course of ceftazidime).

The mean AWP of cefepime is $21.37 per gram (range, $18.30 to $31.87 per gram).[48] Based on a daily dose requirement of 6 g with intermittent infusion versus 5 g with continuous infusion,[23] continuous-infusion cefepime would reduce the costs associated with this antibiotic by an estimated $299.18 for a 14-day treatment course and by an estimated $448.77 for a 21-day treatment course. Based on annual hospitalization rates for CF pulmonary exacerbations, this is equal to a total annual reduction in medication costs of approximately $5.5 million (assuming all regimens include a 14-day course of cefepime), or approximately $8.3 million (assuming all regimens include a 21-day course of cefepime).

Because the acquisition cost is typically less than the AWP, the true reduction in medication costs is expected to be slightly less than that estimated in the preceding paragraph. Further, these reductions in costs are based on using the minimum dose necessary to achieve a C_{ss} that exceeds the MIC. To ensure an optimal C_{ss}, some clinicians may use larger daily doses than those studied, thereby lessening the pharmacoeconomic effect of the medication acquisition cost.

The cost of treating a patient with a CF exacerbation in the hospital is significantly higher than the cost of treating at home.[49] Continuous-infusion beta-lactam therapy may be administered in the ambulatory setting via a portable infusion pump, thereby decreasing the significant costs associated with inpatient treatment, including but not limited to the time required for medication preparation in the pharmacy and for medication administration by nursing staff.[17,20] However, patients in the ambulatory setting may be less likely to receive optimal intensive chest physiotherapy and respiratory medication treatments than patients who are admitted to the hospital. Therefore, the Cystic Fibrosis Foundation has recommended that IV antibiotic treatment not be provided in the outpatient setting unless resources and support equivalent to the hospital setting can be ensured.[6]

QUALITY-OF-LIFE CONSIDERATIONS

Little information is available regarding the effect of continuous-infusion beta-lactam therapy on quality of life in patients with CF. Patients with a pulmonary exacerbation often need to spend 2 to 4 weeks in the hospital, resulting in missed school, work, and social activities. Some CF care centers start therapy in the hospital and, upon patient improvement, complete the therapy in the ambulatory setting. A treatment regimen that facilitates early discharge and simplifies home antibiotic treatment would likely be well received by patients.

Continuous-infusion beta-lactam and monobactam treatment eliminates the need for dosing every 6 to 8 hours, and when administered via a portable pump, continuous infusion may facilitate ambulatory treatment. In a small crossover study, 14 pediatric patients with CF were treated in the hospital with once-daily extended-interval amikacin and ceftazidime, administered either three times daily or via continuous infusion via a portable infusion pump. All of the patients preferred the continuous-infusion regimen, with the caveat that it be administered at home.[19]

In another crossover study, 57 children and adults with CF were treated either at home or in the hospital with extended-interval tobramycin, administered once daily over 30 minutes, and ceftazidime, administered either three times daily or via continuous infusion by a portable infusion pump. Patients were treated in the same setting for each treatment course; thus, patients treated with intermittent-infusion dosing at home received continuous-infusion dosing at home, and patients treated with intermittent-infusion dosing in the hospital received continuous-infusion dosing in the hospital. Quality-of-life scores, which were assessed by a validated CF questionnaire,[50] were similar for the two regimens, but 82% of patients preferred the continuous-infusion regimen.[17]

The effect of continuous-infusion beta-lactam therapy on quality of life merits further investigation and should be an outcome in future studies.

CONCLUSION

Continuous infusion has the potential to optimize the efficacy and safety of antimicrobial treatment during CF pulmonary exacerbations while potentially decreasing the costs of therapy. Compared with intermittent infusion, continuous infusion at normal daily doses is more likely to achieve optimal T > MIC pharmacodynamic goals for intermediate and borderline resistant organisms with an MIC of up to 16 mg/L.

Although the results of studies comparing the efficacy and safety of continuous-infusion and intermittent-infusion antipseudomonal beta-lactam therapy are promising, there is insufficient evidence to recommend the routine use of continuous infusion for patients with pulmonary exacerbations, which supports the position of the Cystic Fibrosis Foundation on this matter. However, continuous-infusion dosing with cef-

tazidime does appear to be a reasonable option for patients who have not responded to traditional dosing methods or who have multidrug-resistant *P. aeruginosa* isolates.

Continuous-infusion beta-lactam treatment, when given via a portable pump, may facilitate ambulatory therapy, thereby reducing the time patients spend in the acute-care setting. Moreover, continuous-infusion beta-lactam treatment (when combined with extended-interval aminoglycoside dosing) is preferred by patients with CF, and it may have a positive impact on quality of life.

Ceftazidime should be given with a loading dose of approximately 50 mg/kg, up to 2 g, followed by continuous infusion with a dosage of 200 mg/kg per day, up to 12 g daily. The maximum dose of 12 g aligns with the dosing regimen used by Hubert et al.[17] If ceftazidime is administered in the ambulatory setting, resources and support equivalent to the hospital setting must be ensured.

The variable stability of ceftazidime and other beta-lactams limits their usefulness for continuous infusion under normal storage conditions. When ceftazidime is given by continuous infusion via a portable infusion pump carried close to the body, as in the ambulatory setting, cold packs should be used to store the drug throughout the infusion, or the medication cartridge should be changed every 8 hours. Because studies assessing the efficacy and safety of other antipseudomonal beta-lactams via continuous infusion in CF are more limited, dosing recommendations cannot be made.

Future research should assess the efficacy and safety of antipseudomonal beta-lactams administered via portable infusion devices, with studies of beta-lactams that have good stability profiles at body temperature (i.e., piperacillin/tazobactam, ticarcillin/clavulanate, and aztreonam); beta-lactams with acceptable stability profiles at body temperature if the medication cartridge is changed twice daily (i.e., cefepime and doripenem); and beta-lactams having acceptable 24-hour stability at lower temperatures with the concomitant use of cold pouches (i.e., cefepime, ceftazidime, doripenem, and meropenem).

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