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Cefepime and Ceftazidime Safety in Hospitalized Infants

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Abstract

Background—Cefepime and ceftazidime are cephalosporins used for the treatment of serious gram-negative infections. These cephalosporins are used off-label in the setting of minimal safety data for young infants.

Methods—We identified all infants discharged from 348 neonatal intensive care units managed by the Pediatric Medical Group between 1997 and 2012 who were exposed to either cefepime or ceftazidime in the first 120 days of life. We reported clinical and laboratory adverse events occurring in infants exposed to cefepime or ceftazidime and used multivariable logistic regression to compare the odds of seizures and death between the 2 groups.

Results—A total of 1761 infants received 13,293 days of ceftazidime, and 594 infants received 4628 days of cefepime. Laboratory adverse events occurred more frequently on days of therapy with ceftazidime compared with cefepime (373 vs. 341 per 1000 infant days, $p < 0.001$). Seizure was the most commonly observed clinical adverse event, occurring in 3% of ceftazidime-treated infants and 4% of cefepime-treated infants ($p = 0.52$). Mortality was similar between the ceftazidime and cefepime groups (5% vs. 3%, $p = 0.07$). There was no difference in the adjusted odds of seizure (odds ratio [OR] = 0.96 [95% confidence interval, 0.89–1.03]) or the combined outcome of mortality or seizures (OR = 1.00 [0.96–1.04]) in infants exposed to ceftazidime vs. those exposed to cefepime.

Conclusions—In this cohort of infants, cefepime was associated with fewer laboratory adverse events than ceftazidime, although this may have been due to a significant difference in clinical exposures and severity of illness between the 2 groups. There was no difference in seizure risk or mortality between the 2 drugs.

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Cephalosporins are one of the most widely used classes of antibiotics. Their broad spectrum, which includes both gram-positive and gram-negative organisms, coupled with an overall low toxicity profile have made cephalosporins a popular choice for both targeted and empiric therapy.¹

Cefepime is approved by the U.S. Food and Drug Administration (FDA) for use in children and infants >2 months of age, while ceftazidime is approved for use in children and infants >1 month of age. Both drugs have been shown to be similarly efficacious in treating a variety of infections in older infants and children.²⁻⁴ In these studies, the safety profiles appear similar, with rash, fever, diarrhea, vomiting, and elevation in hepatic transaminases being the most commonly observed side effects. However, despite the available data in children and older infants, little is known about the safety profile of either drug in young infants.

Neurotoxicities, including seizure, occur with both drugs.⁵ Life-threatening and fatal occurrences of encephalopathy, seizure, and non-convulsive status epilepticus have been reported in both children and adults treated with cefepime and ceftazidime.⁵ Neurotoxicity is included on both FDA labels as a potential adverse event (AE), with specific attention in patients with renal failure. In children, the incidence of neurotoxicity appears to be low,^{2-4, 6-8} but few data regarding neurotoxicity risk are available in young infants.

Given the paucity of safety data in young infants and the use of these extended-spectrum cephalosporins in this population, we sought to compare the safety profile of cefepime and ceftazidime in infants using a large multicenter database.

METHODS

Data Source and Definitions

We identified all infants discharged from 348 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group between 1997 and 2012 who were treated with either cefepime or ceftazidime in the first 120 days of life and who had at least 1 positive culture from the blood, urine (obtained by in-and-out catheter or suprapubic tap), or cerebrospinal fluid (CSF) on the first day of cefepime or ceftazidime therapy or up to 5 days prior to the first dose of these antibiotics. The study was limited to infants with a positive culture to minimize the baseline differences in acuity of illness between the cohorts. We included only the first course of therapy with either cefepime or ceftazidime for each infant. We excluded infants with major congenital anomalies. The data were obtained from an electronic health record that captures information from daily notes written by clinicians and includes maternal history, demographics, medications, microbiology results, laboratory results, diagnoses, and procedures. Medication dosing amounts and interval were not recorded.

We categorized infants according to the cephalosporin received. We defined a course of cefepime or ceftazidime as any number of uninterrupted days of therapy with either drug. We defined inotropic and mechanical ventilator support as therapy with any inotrope (amrinone, dobutamine, dopamine, epinephrine, milrinone, norepinephrine, or

phenylephrine) or invasive mechanical ventilation on a day of therapy with cephalosporins. We defined small for gestational age (SGA) as <10th percentile for age as previously reported by Olsen et al.⁹ We excluded positive cultures from organisms considered contaminants, including non-speciated streptococci, *Bacillus* spp., gram-positive rods (not including *Listeria* spp.), *Lactobacillus* spp., *Micrococcus* spp., *Stomatococcus* spp., and *Bacteroides* spp. Coagulase-negative staphylococci (CoNS) were included if there were 2 positive cultures for CoNS within a 4-day period, 3 positive cultures for CoNS within a 7-day period, or 4 positive cultures for CoNS within a 10-day period. Multiple positive cultures for the same organism within a 21-day period were considered a single infectious episode.

The primary outcome measure for the study was the incidence of clinical and laboratory AEs in the 2 groups. An AE was attributed to cefepime or ceftazidime if it occurred on a day of therapy with either drug. AEs included laboratory and clinical AEs (surgical necrotizing enterocolitis [NEC], medical NEC, focal intestinal perforation, grade III–IV intraventricular hemorrhage [IVH], periventricular leukomalacia, seizures, hyperbilirubinemia requiring exchange transfusion, and rash). Each new clinical diagnosis occurring during treatment with either drug was counted as a separate AE. Laboratory AEs were categorized as an AE or a severe adverse event (SAE) based on pre-specified cut-off values (Table 1). Each laboratory abnormality was counted as a separate AE or SAE and was counted each day that it occurred during therapy with either cefepime or ceftazidime. We defined concomitant antibiotic use as any antibiotic administered on a day of therapy with either cefepime or ceftazidime.

Statistical Analysis

We used standard summary statistics, including counts and percentages and means, medians, and percentiles, to describe categorical and continuous study variables. We compared infant characteristics including baseline severity-of-illness surrogates (mechanical ventilator and inotropic support) between infants receiving cefepime and those receiving ceftazidime using chi-square tests of association and Wilcoxon rank sum tests where appropriate. Fisher's exact test was used to compare each categorical variable. We reported AEs occurring while on cefepime or ceftazidime as both number of days with an AE per 1000 infant days of exposure and the proportion of infants exposed to either drug who suffered an AE at least once while receiving the drug.

We used multivariable logistic regression to evaluate the association between therapy with cefepime vs. ceftazidime and the odds, at the infant level, of AEs, seizure, mortality, and the combined outcome of seizures or mortality while on therapy. We used standard tests and graphing techniques to evaluate all model assumptions. In addition to cephalosporin type, the final model included the following covariates: gestational age, SGA status, therapy with inotropes while on cefepime or ceftazidime, need for mechanical ventilation while on cefepime or ceftazidime, postnatal age at the time of first treatment with cefepime or ceftazidime, and year of discharge. We considered $p < 0.05$ statistically significant. No adjustments were made for multiple comparisons. All analyses were performed using Stata 12 (College Station, TX). The study was approved by the Duke University Institutional

Review Board without the need for written informed consent as the data were collected without identifiers.

Comparison to More Established Cephalosporin: Cefotaxime

Cefotaxime is a more frequently used cephalosporin with a more established safety profile in the neonatal population. Therefore, laboratory and clinical AEs in infants receiving cefotaxime were also compared with those in infants receiving cefepime and ceftazidime.

RESULTS

We identified 2355 infants and 17,921 days of therapy with either cefepime or ceftazidime. Of those, 1761 infants (75%) received ceftazidime for 13,293 days (74%), and 594 infants (25%) received cefepime for a total of 4628 days (26%) (Table 2). The median gestational age for those who received ceftazidime was 26 weeks (interquartile range; 25, 29) vs. 27 weeks (25, 30) for those receiving cefepime ($p=0.12$), and median birth weight was 865 g (680, 1255) for those on ceftazidime vs. 909 g (700, 1318) for those on cefepime ($p=0.08$). Median postnatal age at the time of first antibiotic exposure was 16 days (10, 27) for those receiving ceftazidime vs. 18 days (9, 30) in the cefepime group ($p=0.08$). Infants more often required inotropic and mechanical ventilator support and had a new positive culture on days of therapy with ceftazidime compared with cefepime (12% vs. 10%, $p<0.001$; 60% vs. 49%, $p<0.001$; 6% vs. 5%, $p=0.02$).

There was no statistically significant difference in the microbiological distribution of organisms isolated in cultures between the 2 groups. Thirty-eight infants (2%) in the ceftazidime group had positive CSF cultures vs. 20 infants (3%) in the cefepime group ($p=0.10$).

The overall incidence of any laboratory AEs and SAEs was higher in the ceftazidime group (373/1000 infant days vs. 341/1000 infant days, $p<0.001$, and 112/1000 infant days vs. 87/1000 infant days, $p<0.001$, respectively). The majority of this difference was due to differences in the incidence of complete blood count AEs (331/1000 infant days vs. 300/1000 infant days, $p<0.001$) and SAEs (88/1000 infant days vs. 58/1000 infant days, $p<0.001$) (Table 3). There was a higher incidence of leukopenia (AE) and thrombocytopenia (both AE and SAE) in the ceftazidime group (29/1000 infant days vs. 23/1000 infant days, $p=0.03$; 225 vs. 202, $p=0.001$; 43 vs. 24, $p<0.001$). Among electrolyte abnormalities, only hyperkalemia AEs were more frequent on days of therapy with ceftazidime compared with cefepime (32/1000 infant days vs. 21/1000 infant days, $p<0.001$).

The overall incidence of clinical AEs in the cohort was 14/1000 infant days. There were no significant differences between the ceftazidime and cefepime groups in clinical AEs overall (14/1000 infant days vs. 13/1000 infant days, $p=0.63$, respectively) (Table 4). The most common clinical AEs in both the ceftazidime and cefepime groups were seizure (4/1000 infant days vs. 5/1000 infant days, $p=0.52$), grade III or IV IVH (3/1000 infant days vs. 3/1000 infant days, $p=0.74$), and medical NEC (3/1000 infant day vs. 3/1000 infant days, $p=0.77$). There was no difference in the proportion of infants who suffered a seizure while exposed to ceftazidime vs. cefepime (3% vs. 4%, $p=0.52$). Overall, 18 infants (3%) died

while on cefepime vs. 84 infants (5%) while on ceftazidime ($p=0.07$). There was no difference in the adjusted odds ratio for adverse events, seizure, death, or the combined outcome of seizure and death (Table 5).

During this same time period, there were 4538 infants who received a total of 34,448 days of cefotaxime therapy. The median gestational age was 29 weeks (26, 33), and the median birth weight was 1165 g (806, 1920), which was not statistically different from the other 2 groups. The incidence of laboratory AEs and SAEs was significantly lower in infants receiving cefotaxime (297/1000 infant days and 74/1000 infant days, $p < 0.001$) than in those receiving cefepime or ceftazidime. However, the overall incidence of clinical AEs was not statistically different for those in the cefotaxime group (14/1000 infant days, $p=0.67$) compared with the cefepime (13/1000 infant days) and ceftazidime (14/1000 infant days) groups. The incidence of seizures, specifically, was also no different in the cefotaxime group (5/1000 infant days, $p=0.67$) compared with the cefepime (5/1000 infant days) and ceftazidime (4/1000 infant days) groups. Finally, there was no difference in the adjusted odds ratio for adverse events, seizure, death, or the combined outcome of seizure and death compared to the other 2 groups.

DISCUSSION

This is the largest study to date examining the safety of cefepime and ceftazidime use in young infants. Laboratory adverse events (both AEs and SAEs) were more frequent in the ceftazidime group compared with the cefepime group. This was largely due to significant differences in leukocytosis, thrombocytopenia, and leukopenia. Although the incidence of laboratory AEs was higher in the ceftazidime group, this difference did not persist on adjusted analysis. One potential explanation for this observation is that there were significant differences between the cefepime and ceftazidime groups with respect to clinical exposures and indicators of severity of illness. Specifically, there was greater use of inotropic support and mechanical ventilation, as well as a greater number of positive blood cultures in the ceftazidime group, suggesting a higher level of baseline illness in the ceftazidime group that would predispose these infants to a higher risk of laboratory AEs. There was no difference in the incidence of clinical AEs, which were infrequent, occurring in only 1% of infant days in both groups. This is in contrast to prior studies done in older infants, which have shown a similar incidence of AEs in children receiving cefepime compared with third-generation cephalosporins.^{2-4, 7}

The most commonly observed clinical AE was seizure; seizures occurred in 4% of infants on cefepime, a drug for which seizures have not been consistently reported as an AE in large trials with older children.^{2-4, 6-8, 10} Consistent with previous studies,^{4, 5, 7} the incidence of seizure in the ceftazidime group was 3%. In our study, there was no significant difference in seizure risk between the cefepime and ceftazidime groups. Neurotoxicity has been raised as a concern with cefepime, resulting in a safety announcement by the FDA in June 2012 cautioning dose adjustment in the setting of renal failure and close monitoring for signs of seizure or encephalopathy.¹¹ Similarly, the FDA label for ceftazidime includes neurotoxicity as a potential adverse event.¹² In a recent study examining the incidence of seizure among infants exposed to antimicrobial therapy, seizures occurred in 5.4% (3.0 per 1000 infant

days) and 7.8% (2.3 per 1000 infant days) of infants treated with imipenem/cilastatin and meropenem, respectively.¹³ This group of infants could be considered a reasonable comparator given that carbapenem therapy is often necessary in the setting of significant illness, much like cefepime and ceftazidime.

The strengths of our study include a large, diverse, multicenter cohort of infants. With this large sample size, we were able to examine differences among relatively rare outcomes (e.g., mortality, seizures) between ceftazidime and cefepime. In addition, we were able to compare outcomes with cefotaxime as a “standard” comparator and found no major differences in the incidence of clinical AEs. Our study is limited by its use of electronic medical record data rather than a prospective, randomized clinical trial. We were only able to describe associations between AEs and drug exposure, not infer causality. We did not adjust for laboratory AEs present prior to initiation of therapy with ceftazidime or cefepime. Additionally, we did not adjust for multiple comparisons. This potentially could result in higher apparent incidences of AEs associated with these antibiotics. Also, frequency of laboratory checks were only obtained at the discretion of the individual providers. Additionally, seizure diagnosis was based on physician reporting rather than use of electroencephalogram-confirmed seizures. Despite an attempt to control for baseline differences between the groups, the analysis is susceptible to unmeasured confounders given the lack of randomization. Finally, we did not have access to data on dosing amount and interval, limiting our ability to evaluate an infant’s drug exposure and incidence of safety events.

Our study suggests that the safety profile of cefepime is similar to that of ceftazidime in the neonatal population. Additional studies are needed to further evaluate the safety and dosing of cefepime and ceftazidime in young infants and to determine the potential seizure risk in this vulnerable population.

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TABLE 1**Laboratory Cut-offs for AEs and SAEs**

	AE value	SAE value
Serum electrolytes		
Hyperglycemia	>250 mg/dL	>400 mg/dL
Hypoglycemia	<40 mg/dL	<20 mg/dL
Hypernatremia	>155 mmol/L	>160 mmol/L
Hyponatremia	<125 mmol/L	<115 mmol/L
Hyperkalemia	>6 mmol/L	>7.5 mmol/L
Hypokalemia	<3 mmol/L	<2.5 mmol/L
Hypercalcemia (iCa)	>12.5 mg/dL (>1.5 mmol/L)	>13.5 mg/dL (>1.6 mmol/L)
Hypocalcemia (iCa)	<6.0 mg/dL (<0.9 mmol/L)	<5.0 mg/dL (<0.8 mmol/L)
Renal dysfunction		
Elevated BUN	>70 mg/dL	>100 mg/dL
Elevated creatinine	>1.7 mg/dL	>3.0 mg/dL
Liver dysfunction		
Elevated AST	>600 U/L	>1200 U/L
Elevated ALT	>225 U/L	>450 U/L
Elevated GGT	>90 U/L	>180 U/L
Direct bilirubinemia	>5 mg/dL	>10 mg/dL
Complete blood count		
Leukocytosis	>25,000/mm ³	>40,000/mm ³
Leukopenia	<5000/mm ³	<2000/mm ³
Neutropenia	<500/mm ³	<100/mm ³
Thrombocytopenia	<100/mm ³	<30/mm ³
Thrombocytosis	>600,000/mm ³	>1,000,000/mm ³

AE indicates adverse event; SAE, severe adverse event; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma glutamyl transferase.

TABLE 2

Demographics

		Exposed to cefepime (N=594)	Exposed to ceftazidime (N=1761)	P
Gestational age, weeks				0.45
	<26	209 (35%)	669 (38%)	
	26–28	182 (31%)	547 (31%)	
	29–32	120 (20%)	343 (19%)	
	33–36	52 (9%)	131 (7%)	
	37	31 (5%)	70 (4%)	
Birth weight, g				0.14
	<1000	328 (55%)	1077 (61%)	
	1000–1499	149 (25%)	380 (22%)	
	1500–2499	78 (13%)	196 (11%)	
	2500–3499	29 (5%)	75 (4%)	
	3500	10 (2%)	30 (2%)	
Race/ethnicity				0.02
	White	232 (40%)	742 (44%)	
	African American	163 (28%)	529 (31%)	
	Hispanic	159 (27%)	359 (21%)	
	Other	27 (5%)	72 (4%)	
Male		331 (56%)	998 (57%)	0.68
Caesarean section		364 (62%)	1045 (60%)	0.42
Age at first antibiotic exposure, days				0.03
	<3	43 (7%)	88 (5%)	
	3–6	52 (9%)	129 (7%)	
	7–29	341 (57%)	1134 (64%)	
	30–59	124 (21%)	322 (18%)	
	60–120	34 (6%)	88 (5%)	
Small for gestational age		96 (16%)	283 (16%)	0.97

TABLE 3
Laboratory AEs and SAEs Associated with Cefepime and Ceftazidime, per 1000 Infant Days

	AE			SAE		
	Cefepime	Ceftazidime	P	Cefepime	Ceftazidime	P
Serum electrolytes	86	89	0.55	24	21	0.28
Hyperglycemia	2	3	0.22	0.2	0.5	0.48
Hypoglycemia	7	7	0.93	2	1	0.18
Hypernatremia	7	8	0.57	0	0.5	0.12
Hyponatremia	6	8	0.44	0.2	0.4	0.61
Hyperkalemia	21	32	<0.001	3	4	0.28
Hypokalemia	10	13	0.10	2	2	0.83
Hypercalcemia	2	1	0.14	0.4	0.8	0.39
Hypocalcemia	11	9	0.30	10	6	0.01
Renal function	21	20	0.46	5	6	0.90
Elevated BUN	14	9	0.01	2	2	0.96
Elevated creatinine	13	15	0.34	3	3	0.94
Liver function tests	22	19	0.31	5	6	0.59
Elevated AST	0	0.2	0.31	0	0.1	0.55
Elevated ALT	1	0.5	0.14	0.2	0.2	0.97
Elevated GGT	4	6	0.20	2	2	0.76
Hyperbilirubinemia	18	14	0.07	3	4	0.53
Complete blood count	300	331	<0.001	58	88	<0.001
Leukocytosis	89	103	0.004	22	34	<0.001
Leukopenia	23	29	0.03	3	4	0.34
Neutropenia	4	6	0.31	0.6	0.4	0.45
Thrombocytopenia	202	225	0.001	24	43	<0.001
Thrombocytosis	4	4	0.88	0.2	0	0.09
Any laboratory event	341	373	<0.001	87	112	<0.001

AE indicates adverse event; SAE, severe adverse event; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma glutamyl transferase.

TABLE 4

Clinical Adverse Events Associated with Cefepime and Ceftazidime, per 1000 Infant Days

	Cefepime	Ceftazidime	P
Necrotizing enterocolitis – medical	3	3	0.77
Necrotizing enterocolitis – surgical	1	2	0.23
Focal intestinal perforation	0	0.2	0.31
Grade III–IV intraventricular hemorrhage	3	3	0.74
Seizure	5	4	0.52
Periventricular leukomalacia	0.2	0.5	0.39
Rash	0.6	0.5	0.61
Hyperbilirubinemia requiring exchange transfusion	0	0.1	0.55
Any clinical adverse event	13	14	0.63

TABLE 5

Safety Outcomes in Infants Exposed to Ceftazidime Relative to Cefepime*

	Adjusted odds ratio (95% confidence interval)
Any AE (clinical or laboratory)	1.00 (0.96, 1.03)
Any clinical AE	1.01 (0.96, 1.05)
Any laboratory AE	1.00 (0.97, 1.03)
Seizure	0.96 (0.89, 1.03)
Death	1.02 (0.98, 1.07)
Death or seizure	1.00 (0.96, 1.04)

AE indicates adverse event.

* Adjusted for gestational age, small for gestational age, inotropic support, mechanical ventilator support, postnatal age at exposure, and year of discharge.