

Rate and Incidence of Adverse Reactions Associated With Ceftaroline Exposure: Importance of Cutaneous Manifestations

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Abstract

Background: Ceftaroline is a broad-spectrum, methicillin-resistant *Staphylococcus aureus* (MRSA)-active β -lactam approved for acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired pneumonia. Because of its favorable spectrum and pharmacokinetics, ceftaroline is frequently utilized for infections such as osteomyelitis and endocarditis. Ceftaroline has been associated with neutropenia, but evaluation of other adverse events remains limited.

Objective: To describe the rates and types of ceftaroline-associated adverse events and determine if patients' baseline allergies affect the rates of an adverse event. **Methods:** A single-center, retrospective, observational analysis was conducted of all patients who received ceftaroline between November 4, 2011, and March 28, 2017, at the VA Saint Louis Health Care System. The Naranjo algorithm was utilized as a standardized method to evaluate likelihood that the adverse events were caused by ceftaroline therapy. Ceftaroline dose, duration, indication, and baseline allergy information were collected for all patients. **Results:** There were 75 patients who received 78 courses of ceftaroline identified for inclusion. The most common indications were osteomyelitis (51.3%) and ABSSSI (16.7%). Overall, 13/75 (17.3%) patients developed an adverse event, and 10/75 (13.3%) required discontinuation of ceftaroline. Rash was the most common adverse reaction and occurred in 7/75 (9.3%) patients, followed by neutropenia in 3/75 (4.0%) patients. There were no differences in baseline allergy characteristics between patients who experienced an adverse reaction to ceftaroline and those who did not. **Conclusions:** When compared with clinical trials, ceftaroline use appears to be associated with an increased rate of overall adverse events, which is driven by cutaneous reactions.

Keywords

ceftaroline, adverse events, toxicity, neutropenia, rash

Introduction

Ceftaroline is a broad-spectrum, methicillin-resistant *Staphylococcus aureus* (MRSA)-active cephalosporin antibiotic approved by the US Food and Drug Administration (FDA) in October 2010 for acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired pneumonia.¹ Because of its broad spectrum, favorable pharmacokinetic profile, and convenient administration, off-label prolonged (>14 days) ceftaroline has been used clinically for the treatment of osteomyelitis, bacteremia, and infective endocarditis.^{2–4} The prolonged use of ceftaroline therapy has been associated with neutropenia, based on case reports, case series, and 2 observational analyses.^{5–10}

The first case report of ceftaroline-induced neutropenia was published in 2013⁵; since this time, there have been additional reports of ceftaroline-associated adverse events, with rates ranging from 10% to 75% of patients treated

with prolonged therapy.^{6–10} Most of the current literature regarding prolonged ceftaroline adverse events focuses on hematological effects, specifically neutropenia^{5–9}; in fact, only 1 publication to date includes a detailed analysis of cutaneous manifestations.¹⁰ Furthermore, the majority of the currently published literature does not include information about patients' baseline allergy information, which may be important when evaluating ceftaroline adverse events because patients with 1 drug allergy have been shown to have an increased risk of experiencing a separate drug reaction.¹¹

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At the VA Saint Louis Health Care System, ceftaroline use is restricted to initiation by the infectious diseases interdisciplinary team and is utilized for the treatment of both labeled and off-label infectious etiologies. Through anecdotal observations, the overall rate of any adverse event with prolonged ceftaroline exposure appeared elevated when compared with other antimicrobials. However, this elevation appeared to be driven by cutaneous manifestations rather than development of hematological abnormalities, which are widely described. Given the above anecdotal observations, the objective of this analysis was to describe ceftaroline-associated adverse event types and rates at our institution and determine if a patient's baseline allergies had any impact on the development of an adverse event.

Methods

All patients who had received at least 1 dose of ceftaroline from FDA approval on October 29, 2010, through March 28, 2017, were identified through pharmacy records. All courses of ceftaroline were manually reviewed by an infectious diseases pharmacist (JWJ) for development of an adverse event and, if identified, whether ceftaroline therapy was discontinued or not. All information was obtained through the Veteran's Affairs electronic medical record, computerized patient record system. Documentation of an adverse event caused by ceftaroline must have been entered or confirmed in a patient's electronic medical record (allergies, progress note, etc) by the treating infectious diseases attending, fellow, or pharmacist during the course of therapy. Because ceftaroline requires infectious diseases initiation and follow-up at our institution, all patients had lab work evaluated by an infectious diseases pharmacist at least weekly and were evaluated by an infectious diseases physician at least twice (initiation and planned end of therapy) while on ceftaroline therapy.

An adverse event was defined and classified as one of the following: (1) rash—determined based on manual chart review of physical examination documentation by a provider or home health nurse and subsequently confirmed by the infectious diseases interdisciplinary team; (2) neutropenia—new onset absolute neutrophil count of ≤ 1500 cells/ μL after ceftaroline initiation; (3) acute kidney injury—2-fold increase in serum creatinine or $\geq 50\%$ decrease in creatinine clearance (Cockcroft-Gault) during ceftaroline therapy; (4) eosinophilia—new-onset absolute eosinophil count ≥ 500 cells/ μL after ceftaroline initiation; (5) thrombocytopenia—new-onset platelet count $\leq 150\,000/\mu\text{L}$ after ceftaroline initiation; (6) anemia—decrease in hemoglobin by ≥ 2 g/dL from baseline after ceftaroline initiation; or (7) other—a documented adverse event in the patient's electronic medical record determined to be secondary to ceftaroline therapy that does not meet criteria as above. All patients were reviewed from date of ceftaroline initiation until 2 weeks after completion of therapy.

All adverse reactions were additionally evaluated utilizing the Naranjo algorithm¹² and required a score of at least 4 to be included. According to the Naranjo algorithm (range 0-13), a medication's association with an adverse event is as follows: score of <2 is doubtful, score of 2 to 4 is possible, score of 5 to 8 is probable, score of ≥ 9 is definite.¹² A score of 4 was allowed for inclusion only if the answer to question 5 on the Naranjo algorithm ("Are there alternative causes that could have caused the reaction?") was "yes" because this would remove a point in the Naranjo scale.¹² Additionally, for a patient with a score of 4 to be included, at least 1 member of the infectious diseases interdisciplinary team must have reviewed the case at the time of the adverse reaction and documented the adverse event to be directly associated with ceftaroline therapy in the patient chart.

Ceftaroline dose, duration, and indication were collected for all patients. Ceftaroline dose was determined to be high dose (600 mg every 8 hours, or equivalent for renal function) or standard dose (600 mg every 12 hours, or equivalent for renal function). Additionally, patients' baseline allergy information was obtained from the electronic medical record if documented as either an observed or self-reported/historical event. Allergies were categorized into the following groups: no allergies, nonantibiotic allergies, and antibiotic allergies. For patients with antibiotic allergies, the specific agent(s) were documented. The total number of individually documented allergies was recorded for all patients.

Demographic data are described as frequencies or medians, as appropriate. Statistical analysis between patients who did and did not experience a ceftaroline-associated adverse event were completed utilizing χ^2 or Fisher's exact test as appropriate. All statistical testing was performed using IBM-SPSS version 22.0 (IBM Corp, Armonk, NY). This review and analysis was approved by the VA Saint Louis Institutional Review Board.

Results

Ceftaroline was first administered on November 4, 2011, at the VA Saint Louis Health Care System. Between this date and March 28, 2017, ceftaroline was utilized 78 times in 75 patients. Demographic information for all ceftaroline exposures are displayed in Table 1.

There were 14 adverse events reported in 13/75 (17.3%) patients, all of which were associated with a Naranjo algorithm score of ≥ 4 ; 10 (13.3%) patients required ceftaroline discontinuation secondary to the adverse event. The median duration of therapy in patients who experienced an adverse event was 35 days (interquartile range [IQR] = 7-40), and only 1/13 (7.8%) of these patients had received high-dose therapy. The crude incidence rates of any adverse event, and an adverse event requiring discontinuation, per 1000 patient-days on ceftaroline therapy were 6.57 and 5.05, respectively. Overall, rash was the most common adverse event encountered, which

Table 1. Patient Demographics of Total Ceftaroline Exposures (n = 78).

Characteristic	Value
Median age (years), IQR	63 (58-71.3)
Male (%)	78 (100)
Ethnicity (%)	
White	64 (82.1)
Black	14 (17.9)
Baseline allergies (%)	
No allergies	30 (38.5)
Nonantibiotic allergy	31 (39.7)
Antibiotics	17 (21.8)
β -Lactam	14
Non- β -lactam	3
Median number of baseline allergies, IQR	1 (0-2)
Median duration of ceftaroline therapy (days), IQR	33 (6-41)
Primary indication for therapy ^a (%)	
Osteomyelitis	40 (51.3)
ABSSSI	13 (16.7)
Pneumonia	7 (9.0)
Bloodstream infection	7 (9.0)
Infective endocarditis	4 (5.1)
Septic arthritis	3 (3.8)
Prosthetic joint infection	2 (2.6)
Empyema	2 (2.6)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; IQR, interquartile range.

^aOne patient each with a primary diagnosis of osteomyelitis, ABSSSI, pneumonia, and septic arthritis had a secondary diagnosis of bloodstream infection. A single patient with a primary diagnosis of bloodstream infection had a secondary diagnosis of an epidural abscess. A single patient with a primary diagnosis of infective endocarditis had a secondary diagnosis of septic arthritis.

occurred in 7/75 (9.3%) patients followed by neutropenia in 3/75 (4.0%) of patients. One patient experienced an adverse reaction to ceftaroline on his second course of the medication. This patient tolerated a 6-day course for an acute bacterial skin and soft-tissue infection and developed a rash on day 18 of ceftaroline when being treated for osteomyelitis 7 months after the initial exposure (Table 2, patient 3). Additionally, 1 patient experienced both rash and neutropenia while on ceftaroline therapy (Table 2, patient 7). Details regarding the 13 patients who experienced an adverse event are provided in Table 2.

There was no significant difference between the baseline allergies of those patients who experienced an adverse event with ceftaroline therapy and those who did not when compared by allergy classification or by history of a β -lactam allergy (Table 3).

Discussion

Ceftaroline therapy has been associated with neutropenia, especially with prolonged, non-FDA approved courses of therapy.⁵⁻¹⁰ Our analysis is among the largest conducted to

date with 75 patients and 78 ceftaroline exposures included over a 5.5-year period. Furthermore, we evaluated all adverse events associated with ceftaroline therapy as well as included the impact of the patients' baseline allergy information prior to ceftaroline initiation.

Overall, we identified 13 (17.3%) patients who experienced at least a single adverse event after a median of 35 days (IQR = 7-40) of exposure, of whom 10 patients (13.3%) required discontinuation. The adverse event rate described is generally supported by the previously reported literature, which focuses on ceftaroline-induced neutropenia.^{9,10} Unique to our review was the finding that cutaneous adverse events were the most frequently described adverse event to ceftaroline therapy (9.3%). In fact, to date, only 1 additional analysis has included a focused discussion of cutaneous adverse events related to ceftaroline.¹⁰ In this analysis, rash was the most frequently described adverse event when all hematological adverse events were not grouped together, as was done in our analysis.¹⁰ The above observational analysis, in conjunction with our results, suggest that cutaneous manifestations may be a more clinically important adverse reaction with ceftaroline than previously described.

When comparing our data for the incidence of rash with those in the ceftaroline clinical trials, an increased rate was observed. When the data for the CANVAS 1 and 2 trials were pooled for the safety summary, rash was reported in 22/692 (3.2%) of patients.¹³ Unfortunately, the event rate for rash in the FOCUS 1 and 2 trials is not reported in the articles^{14,15} or the integrated safety summary.¹⁶ However, the ceftaroline package insert reports that rash occurs in 3% of the 1300 patients within the pooled analysis of the above 4 FOCUS and CANVAS trials.¹⁷ Additionally, when ceftaroline was studied at high doses (600 mg every 8 hours) in the COVERS trial, the overall rate of rash as an adverse event was 23/506 (4.5%), or 28/506 (5.5%) when including urticarial reactions.¹⁸ In our analysis, rash was observed in 9.3% of patients, which is about 2 to 3 times the reported rates from the clinical trials. This increased rate could potentially be a result of the longer duration of therapy because the clinical trials were limited to 14 days and the median exposure in our population was 35 days.

Ceftaroline exposure has been previously linked to neutropenia,⁵⁻¹⁰ and the patients within our analysis who experienced neutropenia (patients 7-9, Table 3) all experienced profound cases. All 3 patients ultimately had a neutropenia nadir <100 cells/ μ L, with absolute neutrophil count recovery rapidly after the discontinuation of ceftaroline, adding further support to this previously reported adverse event.

When evaluating adverse reactions to a given medication, it is important to evaluate the baseline allergies of the population because data suggest that patients with at least 1 allergy are at increased risk for development of additional allergies.¹¹ Our analysis is only 1 of 2 studies to evaluate the relationship between patients' baseline allergies and development of

Table 2. Ceftaroline Patients With Adverse Events.

	Adverse Event(s) Type	Naranjo Score	Ceftaroline Discontinued	Ceftaroline Duration at AE (days)	High Dose?	Ceftaroline Indication	Description of AE
Patient 1	Rash	5	Y	8	N	Osteomyelitis	Erythematous, pruritic rash on neck and trunk
Patient 2	Rash	6	Y	16	N	Osteomyelitis	Diffuse, erythematous, nonpruritic rash on trunk and upper extremities
Patient 3 ^a	Rash	5	Y	18	N	Osteomyelitis	Diffuse, erythematous, pruritic rash on trunk and bilateral lower extremities
Patient 4	Rash	5	Y	11	N	Empyema	Diffuse maculopapular rash
Patient 5	Rash	7	Y	33	N	Empyema	Fine, diffuse, erythematous, and pruritic rash on trunk and bilateral upper and lower extremities
Patient 6	Rash	4 ^b	Y	34	N	ABSSSI	Diffuse, blanching erythroderma rash on trunk, upper and lower extremities, and face; patient developed oral lesions as well
Patient 7	• Rash • Neutropenia	• 7 • 8	Y	37	Y	Bloodstream infection	• Fine, diffuse, erythematous, and pruritic rash on trunk • ANC nadir = 93 cells/μL • Baseline ANC = 4428 cells/μL
Patient 8	Neutropenia	8	Y	42	N	Osteomyelitis	• ANC nadir = 91 cells/μL • Baseline ANC = 2523 cells/μL
Patient 9	Neutropenia	7	N ^c	41	N	Osteomyelitis	• ANC nadir = 14 cells/μL • Baseline ANC = 6772 cells/μL
Patient 10	Acute kidney injury	5	Y	9	N	Osteomyelitis	• SCR increase from 2.32 to 4.86 mg/dL.
Patient 11	Thrombocytopenia	7	N ^d	43	N	Osteomyelitis	• Platelet nadir = 104 000/μL • Baseline platelets = 271 000/μL
Patient 12	Thrombocytopenia	7	N ^d	38	N	Osteomyelitis	• Platelet nadir = 111 000/μL • Baseline platelets = 204 000/μL
Patient 13	Other	5	Y	1	N	Pneumonia	Bronchospasms

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; AE, adverse event; ANC, absolute neutrophil count; N, No; Y, Yes. SCR, serum creatinine

^aPatient tolerated 6-day course of ceftaroline without adverse reaction for ABSSSI 7 months prior to second exposure.

^bPatient was receiving metronidazole orally at the time of reaction, which was identified as possible alternative cause of adverse event (Naranjo score = 1). Per infectious diseases interdisciplinary team documentation, ceftaroline was determined to be the most likely culprit agent; thus, the patient met inclusion criteria.

^cLab obtained evening of day 41 of therapy. Neutropenia discovered on day 42/42 of therapy. Thus, patient completed therapy rather than having therapy discontinued.

^dPatients were allowed to continue therapy unless platelets dropped below 100 000/μL.

Table 3. Analysis of Adverse Event Rates in Ceftaroline Patients (n = 75).

	No Ceftaroline Adverse Event (n = 62)	Ceftaroline Adverse Event (n = 13)	P Value
Allergy classification (%)			0.206
No allergies	26 (41.9)	3 (23.1)	
Nonantibiotic allergy	25 (40.3)	5 ^a (38.5)	
Antibiotic allergy	11 (17.7)	5 (38.5)	
Specific antibiotic allergies (n/N)			N/A
Penicillin	7/11	2/5	
Sulfamethoxazole/Trimethoprim	2/11	1/5	
Cephalexin	1/11	1/5	
Vancomycin	0/11	1/5	
Multiple antibiotics ^b	1/11	0/5	
Baseline β-lactam allergy (%)	9 (14.5)	3 (23.1)	0.444
Prolonged course: >14 days (%)	23 (37.1)	4 (30.8)	0.334

^aClassification of the patient who tolerated the initial ceftaroline course without adverse reaction.

^bOne patient who did not experience an adverse event with ceftaroline reported baseline allergies to ampicillin/sulbactam, ciprofloxacin, and vancomycin.

adverse reaction to ceftaroline.¹⁰ In our veteran population treated with ceftaroline, there was no difference in rates of adverse events when analyzed by either broad classification (no allergies, nonantibiotic allergies, antibiotic allergies) or when specifically focused on patients with prior reports of β-lactam allergies, which are in agreement with the results reported by Blumenthal et al.¹⁰ Although no association between baseline allergies and ceftaroline adverse events was observed in either analysis, it is important to note that because of the low overall number of events evaluated, no strict conclusions can be arrived at.

Our analysis does have limitations. First, given the retrospective design, the information is directly dependent on the accuracy of documentation. Furthermore, the reporting of adverse events is subjective, with some providers having a lower threshold to report and document than others. To help alleviate both the above risks of bias, we utilized the Naranjo algorithm and an infectious diseases trained pharmacist to help objectively evaluate the probability of an

adverse event truly being associated with ceftaroline therapy. Additionally, because ceftaroline use is restricted to infectious diseases at our institution, all reported ceftaroline-associated adverse events had infectious diseases review at the time of the event. The next limitation includes the observational design, meaning that no conclusions regarding rates of adverse events with ceftaroline compared with other antimicrobials can be deduced, and such conclusions will require future comparative data. Finally, our population consisted of male veterans, and these results may not be generalizable to the overall population. However, our results also did not differ remarkably from other observational analyses published.^{9,10}

To date, and despite the observational data available, there is no analysis that directly compares adverse event rates of ceftaroline with that of another cephalosporin. Given the growing observational evidence, this comparison is necessary to confirm or refute the anecdotal association of increased adverse event rates with ceftaroline exposure.

Conclusion

The rate of ceftaroline-associated adverse events appears to be higher than that reported in clinical trials, which is potentially a result of the off-label use for prolonged durations of therapy. The most frequently observed adverse events were cutaneous reactions, which is possibly overshadowed by neutropenia in the currently available literature. Ultimately, patients receiving ceftaroline, especially off-label and for prolonged durations, should be monitored for laboratory abnormalities and cutaneous reactions.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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