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Early use of ceftaroline fosamil in the United States Veterans Health Care System

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Abstract

Background—Ceftaroline fosamil is U.S. FDA-approved for acute bacterial skin and skin structure infections and community acquired bacterial pneumonia, but it is unknown how ceftaroline is being used in real-world settings or how adverse effects (AEs) and mortality compare to clinical trials.

Objective—This study describes ceftaroline use, AEs, and mortality in U.S. Veterans Health Administration (VHA) hospital patients.

Methods—This phase 4, population-based, epidemiologic study analyzed patients ≥18 years old who received ≥1 ceftaroline dose within 14 days of admission at 69 VHA hospitals in 41 U.S. states/territories from 10/1/10–9/30/14. VHA repository data were linked using unique patient identifiers. Diagnoses and AEs were determined using ICD9-CM and CSS codes. Demographics, AEs within 30 days of therapy initiation, and all-cause in-hospital mortality were summarized using descriptive statistics.

Results—764 patients met study criteria. Patients were 97% male and 56% white, with a median age of 61 years and a Charlson score of 6. Diagnoses included skin (40%), sepsis (30%), osteomyelitis (25%), diabetic foot (22%), pneumonia (16%), bacteremia (11%), endocarditis (6%), meningitis (2%), and device (2%) infections. Ceftaroline was used first-line (37%), second-line (56%), and third-line or greater (7%). Patients received ceftaroline a median of 3 days after hospital admission. All-cause in-hospital mortality rates were: overall (5%), skin (2%), sepsis

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6. Compliance with Ethical Standards

All other authors: none to declare.

7. Authors' contributions

Study concept and design: Frei, Reveles, Lee. Statistical analysis: Frei. Interpretation of data: All authors. Drafting of the manuscript: Britt, Evoy, and Frei. Critical revision of the manuscript for important intellectual content: All authors. Study supervision: Frei.

(9%), osteomyelitis (3%), diabetic foot (1%), pneumonia (13%), bacteremia (6%), endocarditis (11%), meningitis (6%), and device (13%). Eosinophilia, leukopenia, leukocytosis, fibromyalgia, myalgia and myositis, and polymyalgia rates were <1% each.

Conclusions—Ceftaroline is used in VHA hospitals for various diagnoses. Mortality was low and comparable with rates from clinical trials. Additional studies comparing ceftaroline to other drugs used in similar situations are needed.

1. Introduction

Antibiotic resistance poses a significant threat to public health and substantially impacts the United States (U.S.) economy. According to the U.S. Centers for Disease Control and Prevention, each year more than 2 million people in the U.S. contract infections from bacteria that are resistant to at least one appropriate antibiotic, resulting in an additional $20 billion in direct healthcare costs [1]. One of the more prevalent organisms responsible for this phenomenon is *Staphylococcus aureus*. In 2011, 80,461 cases of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections and 11,285 deaths related to MRSA were reported in the U.S. alone [1]. While the number of severe infections in hospitals has been decreasing since 2005, MRSA continues to be a serious threat, displaying an increasing incidence in the general population [1].

Ceftaroline fosamil, approved in 2010 by the U.S. Food and Drug Administration (FDA), is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia [2,3]. It is a cephalosporin antibiotic with an affinity for penicillin binding proteins 2a and 2x, resulting in activity against multiple Gram-positive and Gram-negative organisms [4]. Notably, ceftaroline serves as a significant addition to the current antibiotic armamentarium as the first beta-lactam to demonstrate activity against MRSA, thus providing an additional therapeutic option for resistant bacteria. Ceftaroline was added to the U.S. Veterans Health Administration (VHA) formulary, with restriction, in October 2011.

While ceftaroline has been shown to be efficacious for certain indications in clinical trials, the extent to which it has been integrated into clinical practice is unclear, and little evidence regarding its use, clinical efficacy, or safety in real-world settings is available. Furthermore, studies are needed to evaluate the effectiveness of ceftaroline for infections beyond those initially approved (e.g., bacteremia, endocarditis, and osteomyelitis, among others). Ho and colleagues reported a small case series (n=6) of patients who received ceftaroline as salvage monotherapy for MRSA bacteremia and endocarditis [5]. These patients experienced rapid clearance of bacteremia following ceftaroline therapy. Similarly, Lin and colleagues described 10 patients treated with ceftaroline for severe MRSA infections, including bacteremia, endocarditis, and other deep-seated infections [6]. Ceftaroline was effective for 7 out of 10 of these patients.

In addition, Casapao and colleagues conducted a large analysis of 527 patients who received ceftaroline for a variety of different infections [7]. Of these, 88% achieved clinical success and 92% survived the infection. Finally, Zasowski and colleagues studied 211 patients who

received ceftaroline for MRSA bloodstream infections and found that 68% achieved clinical success [8].

Together, these reports provide promising evidence of the effectiveness of ceftaroline for indications not currently approved by the FDA; however, confirmation of these results in larger cohorts is needed. The objective of this study was to describe ceftaroline use, adverse effects, and health outcomes in a national health system from the date of FDA approval through fiscal year 2014.

2. Methods

This was a population-based epidemiologic study of patients aged 18 years or older who received at least one dose of ceftaroline at any of the hospitals in the Veterans Health Administration (VHA) system in fiscal years 2011 to 2014 (10/1/10 to 9/30/14). Patients who did not receive ceftaroline therapy within 14 days of hospital admission were excluded from the study. Data were obtained from VHA administrative, clinical, laboratory, and pharmacy data repositories and linked using a unique patient identifier. Study variables included patient age, sex, race, selected comorbidities (see Table 1), prior and concomitant antibiotic medications, prior hospitalization in the past 90 days, geographic location of the hospital, infectious disease diagnosis, hospital length of stay, all-cause 30-day hospital readmission, and all-cause in-hospital mortality from date of discharge. The occurrence of eosinophilia, leukopenia, leukocytosis, fibromyalgia, myalgia and myositis, and polymyalgia up to 30 days after ceftaroline initiation were also included. Infectious disease diagnoses, comorbidities, and adverse events were determined using administrative codes (i.e., ICD9-CM and/or Clinical Classifications Software (CCS) codes). Please see Electronic Supplementary Material for details.

The overall ceftaroline population was described. Dichotomous variables were reported as counts and percentages, while continuous variables were summarized using means and standard deviations or medians and IQRs. The ceftaroline population was sub-divided based on infectious disease indication, and each sub-population was described using the same variables.

All data collection and analyses were performed at the South Texas Veterans Health Care System (STVHCS), Audie L. Murphy VA Hospital, San Antonio, Texas, by researchers with VHA appointments. All statistical analyses were conducted using SAS® and JMP®.

3. Results

A total of 1,069 patients were initially identified. After limiting the analysis to only those patients who received ceftaroline within the first 14 days of hospital admission, 764 ceftaroline patients were available for this analysis. Baseline demographics and patient characteristics for the overall cohort are depicted in Table 1. Patients were primarily males (97%) of white race (56%) and older age (median (IQR): 61 (54–67)) with a Charlson score of 6 (median, IQR: 3–8). Overall, patients frequently had a history of hypertension (81%), dyslipidemia (65%), and diabetes without complications (56%). A majority had received

antibiotics in the past 90 days (87%), with a smaller group experiencing a prior hospitalization (40%).

In this analysis, diagnoses in which ceftaroline was utilized included skin (40%), sepsis (30%), osteomyelitis (25%), diabetic foot (22%), pneumonia (16%), bacteremia (11%), endocarditis (6%), meningitis (2%), and device (2%) infections; some patients had more than one diagnosis. Ceftaroline was used in general medicine floors (81%) and ICUs (19%), both as a first-line antibiotic with anti-MRSA activity (37%) and as a second-line antibiotic with anti-MRSA therapy (56%). The typical patient received ceftaroline within 3 days (median, IQR: 1–6) of hospital admission and remained hospitalized for a total of 5 days (median, IQR, 3–12) (Table 2).

All-cause in-hospital mortality rates among patients who received ceftaroline were low (Table 2). Overall, 5% of patients died during hospitalization. Pneumonia and device infections were associated with the highest rates of all-cause in-hospital mortality (13%), and diabetic foot infections were associated with the lowest all-cause in-hospital mortality (1%). Mortality rates by infection type are depicted in Table 2.

Overall, 33% of patients were readmitted to the hospital within 30 days. Those patients who had bacteremia or meningitis on first admission were the most likely to be readmitted to the hospital: bacteremia (48% readmission rate) and meningitis (44% readmission rate).

Ceftaroline was well-tolerated in this population. Rates of eosinophilia, leukopenia, leukocytosis, fibromyalgia, myalgia and myositis, and polymyalgia were found to be less than 1% each during the 30-day period after the start of therapy.

4. Discussion

Currently, only two other epidemiological studies of ceftaroline use in large health systems are available. See Table 3 for a comparison of those studies and this study. Casapao and colleagues conducted a retrospective, medical record review of patients in five non-VHA hospitals in Michigan, Ohio, Florida, and Illinois who were treated with ceftaroline for various infections [7]. Compared to our study, the patient population in the Casapao study had more females (3% in our present study vs 42.5% in Casapao's study), less diabetes mellitus (56% vs 40%), less COPD (33% vs 12.7%), more hemodialysis (2% vs 8.2%), less recent antibiotic use in the past 90 days (87% vs 30%), lower Charlson scores (median score of 6 vs 2), and were about the same age (61 vs 60 years) [7]. Additionally, patients had to have received ceftaroline for at least 72 hours to be included in Casapao's study [7], while our study included patients who received at least one dose of ceftaroline. Casapao described health outcomes in patients who received ceftaroline, including hospital and ICU length of stay, all-cause in-hospital mortality, 30-day hospital readmission, and clinical and microbiological success [7]. Our study analyzed several of the same health outcomes, including hospital length of stay, all-cause in-hospital mortality, and hospital readmission.

Zasowski and colleagues conducted a retrospective, multicenter, observational study of adult patients who received ceftaroline for ≥72 hours for MRSA bloodstream infections in three non-VHA hospitals in Michigan and Florida [8]. Compared to our study, the patient

population in Zasowski's study had more females (3% vs. 44%), less diabetes mellitus (56% vs. 37%), more hemodialysis (2% vs. 21%), lower Charlson scores (median score of 6 vs. 3), and were about the same age (61 vs. 59 years). Additionally, patients had to have received ceftaroline for at least 72 hours to be included in Zasowski's study, while our study included patients who received at least one dose of ceftaroline. Zasowski's study and our study described hospital length of stay and all-cause in-hospital mortality, but Zasowski's study also described clearance and duration of bloodstream infection; however, it did not discuss hospital readmission.

In this study, more than 1,000 VHA patients received ceftaroline in the United States National Veterans Health Care System through fiscal year 2014. We excluded patients who received ceftaroline more than 14 days after hospital admission because we do not believe it is appropriate to attribute health outcomes to ceftaroline when the patient received other, possibly inappropriate, therapy for a long period of time before receiving ceftaroline. Our study is not a "salvage therapy" study, but rather, an "early use" study. Our patients received ceftaroline relatively quickly (<4 days median lag time for all infection types), which is similar to the Casapao ceftaroline epidemiology study (median (IQR): 3 days (1–6)) [7]. Much of the use has been in patients with skin, sepsis, osteomyelitis, diabetic foot, pneumonia, and bacteremia infections. Patients who receive care at VHA facilities are older than many study cohorts (median >60 years for all infection types) and more likely to be male (>90% for all infection types). These patients also have numerous comorbidities, which may complicate treatment decisions and contribute to worse health outcomes.

Median hospital length of stay was variable by infection type with the longest stays attributable to meningitis (9 days IQR (4–34)) and device infections (10 days (3–19)). Overall, median length of hospital stay of 5 days (IQR 3–12) was lower than findings from the Casapao study (median (IQR): 12 days (7–21)) [7]. Other small, non-comparative studies in select infection types demonstrated similar median lengths of stay for ABSSSI (5 days in the present study versus 7–8 days in previous studies) and pneumonia (8 days vs 7 days) [9,10]. One study by Udeani and colleagues that examined ceftaroline for the treatment of pneumonia demonstrated a longer length of stay than the findings presented here (mean of 12.5 days in elderly patients and 16.3 days for younger patients) [11]. However, the population consisted mostly of elderly patients with medical histories related to pneumonia, which could possibly indicate a greater disease severity and longer recovery time.

Our study demonstrated that patients who received ceftaroline had low mortality. Overall, hospital mortality in this study (5%) was similar to results from the Casapao epidemiological study, which was conducted outside of the VHA (7.6%) [7]. Previously available data concerning ceftaroline use in non-FDA approved indications is limited; however, rates of hospital mortality in the current study were comparable to previous research describing ceftaroline use in approved indications like ABSSSI (2% vs 2–2.3%) [9,10] and pneumonia (13% vs 12.5%) [12].

One of the most valuable aspects of our study is that it reports health outcomes by infection type. We found that hospital readmission rates varied greatly by infection type, as expected, with the highest rates among those patients who had bacteremia (48% readmission rate) or

meningitis (44% readmission rate) on first admission, and lowest rates among those patients who had endocarditis (28% readmission rate) or pneumonia (30% readmission rate) on first admission. Reasons for readmission in this study are unknown, so it is possible that patients were readmitted for comorbidities unrelated to their initial infection. Rates of 30-day readmission in this study are higher than those displayed by Casapao and colleagues for patients treated with ceftaroline overall (33% vs 9.1%) [7]. This difference was also seen in different infection types, including bacteremia (36% vs 20–25%) [13], ABSSSI (36% vs 12–14%) [9], and pneumonia (30% vs 9–22.5%) [10,12]. However, this could be due to our study taking place in an integrated, closed health care system; we had readmission information for all hospitals in the VA national health care system, so even if the patient went to a different hospital within the system for their readmission, we were still able to capture that readmission.

Clinical trials of ceftaroline demonstrated low rates of blood and lymphatic system disorders, such as eosinophilia (<2%) [4]. In post-marketing experience, cases of agranulocytosis and leukopenia were reported as well. Two recent studies observed neutropenia in 67 patients when ceftaroline was used ≥2 weeks in duration (10–14% neutropenia) and ≥3 weeks in duration (21% neutropenia) [14]. Another study observed that 18% of their 39 patients experienced neutropenia; patients received ceftaroline for a median of 27 days [15]. Both studies recommended close laboratory monitoring with long-term ceftaroline use. Patients our study experienced low rates of drug-related adverse events (<2% for all infections). In the case of eosinophilia, findings were consistent with ceftaroline clinical trials (<1%). Leukopenia occurred in <1% of patients in our study at 30-days.

This study has limitations. The unique VHA population limits the generalizability of these observations to other health systems. Another limitation is that the specific bacterial pathogens being treated were not retrieved, and thus outcomes regarding ceftaroline efficacy against specific bacterial pathogens cannot be made. However, the primary aim of this study was to provide general information about ceftaroline's pattern of use in a large health system and the clinical outcomes over a period of time not yet studied by other trials. In addition, we do not have information regarding length of ceftaroline therapy, ceftaroline dose, concomitant antibiotic therapies, or reasons for readmission; all of these are vitally important for accurately assessing efficacy and adverse events. Given that we only followed adverse events for 30 days, we cannot comment on long-term safety, including possible bone marrow suppression with longer courses of therapy. Finally, the retrospective design and reliance on consistent, accurate coding within the electronic medical record may result in missing data or misclassification bias for some patients.

However, this study also has many strengths. It offers clinical data from a larger population than any previous post-marketing ceftaroline epidemiology study. The VHA is the largest integrated health care system in the United States, has health care facilities in all 50 states, and maintains an electronic medical record system, which includes administrative, clinical, laboratory, and pharmacy data repositories. As a result, this study offers information on the real-world effectiveness of ceftaroline on health outcomes as opposed to clinical trial situations. Furthermore, the VHA system maintains a vital status file that enables investigators to determine patient mortality, even when it occurs outside the hospital.

Additionally, this study is the first to offer clinical outcomes data for the use of ceftaroline for diabetic foot, meningitis, endocarditis, sepsis, and device infections. As limited information is available investigating the effectiveness of ceftaroline in non-approved FDA indications, this study significantly increases the currently published data regarding use of ceftaroline in these disease states.

Several other studies provide information on clinical success associated with ceftaroline used as monotherapy versus concurrent therapy. While this study did not retrieve information concerning ceftaroline utilization as monotherapy or in combination therapy, this measure reflects real-world practice and would be appropriate to include in future studies.

5. Conclusion

In conclusion, ceftaroline is used in VHA hospitals for many types of infections. Patient mortality was comparable with rates from clinical trials. While this study provides preliminary information on the use of ceftaroline for various infections, further studies are needed to compare these results for ceftaroline versus alternative therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Little evidence is available regarding real-world use and outcomes with ceftaroline.
- Mortality observed in this study was comparable with rates from clinical trials.
- This study increases the published data regarding the use of ceftaroline in disease states for which it does not hold FDA indications, like diabetic foot, meningitis, endocarditis, sepsis, and device infections.

Table 1

Baseline characteristics for patients who received ceftaroline

Variable	All (n=764)	Skin (n=307)	Sepsis (n=233)	Osteo (n=193)	Diab foot (n=170)	Pneumonia (n=124)	Bact (n=87)	Endo (n=46)	Mening (n=18)	Device (n=15)
Age (years), median (IQR)	61 (54–67)	60 (54–66)	61 (55–69)	60 (54–66)	61 (56–66)	62 (56–70)	60 (54–67)	63 (58–73)	61 (58–74)	63 (54–71)
Male, %	97%	96%	97%	98%	98%	98%	98%	98%	94%	100%
Married, %	41%	39%	40%	43%	39%	44%	33%	48%	22%	33%
Charlson Score, median (IQR)	6 (3–8)	6 (3–7)	6 (4–8)	6 (4–8)	6 (4–8)	6 (3–9)	6 (4–9)	5(4–7)	5 (3–8)	8 (5–9)
Selected Comorbidities, %										
Congestive heart failure	25%	26%	29%	22%	26%	28%	30%	43%	22%	40%
COPD	33%	32%	34%	27%	32%	53%	29%	33%	22%	27%
Cerebrovascular disease	14%	11%	17%	14%	11%	17%	18%	22%	6%	20%
Dementia	1%	<1%	2%	1%	0%	2%	5%	4%	0%	7%
Diabetes (complications)	32%	35%	31%	46%	59%	19%	36%	13%	39%	47%
Diabetes (no complications)	56%	63%	55%	72%	99%	41%	61%	41%	61%	53%
Hemi/paraplegia	4%	1%	5%	4%	1%	6%	7%	4%	17%	13%
HIV	1%	2%	1%	1%	1%	2%	3%	2%	0%	0%
AIDS	3%	5%	3%	2%	1%	4%	6%	2%	6%	0%
Liver (mild)	2%	4%	3%	3%	3%	2%	6%	0%	0%	7%
Liver (mod/severe; cirrhosis)	6%	9%	8%	4%	9%	4%	9%	4%	0%	13%
Cancer	19%	13%	21%	17%	14%	26%	17%	20%	22%	33%
Leukemia	3%	3%	6%	2%	1%	7%	2%	2%	0%	0%
Metastatic cancer	4%	2%	4%	3%	1%	8%	3%	0%	0%	7%
Myocardial infarction	9%	7%	12%	9%	8%	10%	14%	17%	17%	27%
Peripheral vascular disease	24%	24%	20%	31%	31%	22%	14%	22%	6%	40%
Renal disease	32%	28%	37%	32%	35%	31%	40%	33%	22%	47%
Dyslipidemia	65%	64%	61%	63%	78%	60%	51%	70%	33%	80%
Hypertension	81%	80%	81%	87%	92%	76%	84%	80%	83%	93%
Hemodialysis	2%	0%	4%	2%	0%	2%	6%	4%	0%	20%
Hospitalization (past 90d), %	40%	36%	41%	47%	37%	41%	49%	43%	44%	53%

Variable	All (n=764)	Skin (n=307)	Sepsis (n=233)	Osteo (n=193)	Diab foot (n=170)	Pneumonia (n=124)	Bact (n=87)	Endo (n=46)	Mening (n=18)	Device (n=15)
Antibiotics (past 90d), %	87%	88%	90%	89%	88%	88%	91%	83%	78%	93%
ICU, %	19%	8%	30%	12%	6%	37%	21%	26%	22%	27%
Weight (lb.), median (IQR)	201 (167–245)	215 (179–261)	195 (164–242)	202 (166–244)	224 (187–277)	179 (151–219)	195 (166–234)	179 (158–212)	210 (184–237)	202 (176–249)

Osteo: osteomyelitis; Diab foot: diabetic foot infections; Bact: bacteremia; Endo: endocarditis; Mening: meningitis; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; ICU: intensive care unit

Table 2

Health outcomes for patients who received ceftaroline

Variable	All (n=764)	Skin (n=307)	Sepsis (n=233)	Osteo (n=193)	Diab foot (n=170)	Pneumonia (n=124)	Bact (n=87)	Endo (n=46)	Mening (n=18)	Device (n=15)
Hosp. LOS, median (IQR)	5 (3–12)	5 (3–9)	6 (3–15)	5 (3–15)	5 (3–7)	8 (3–18)	8 (3–18)	7 (3–14)	9 (4–34)	10 (3–19)
Hosp. Mortality, %	5%	2%	9%	3%	1%	13%	6%	11%	6%	13%
30d Hosp. Readmit, %	33%	36%	36%	35%	38%	30%	48%	28%	44%	40%

Hosp. LOS: hospital length of stay; IQR: interquartile range; Hosp. mortality: hospital mortality

Table 3

Comparison of study design, populations, and outcomes for ceftaroline epidemiology studies

	Casapao et al. [7]	Zasowski et al. [8]	Britt et al.
Sample size, n	527	211	764
Design	Retrospective	Retrospective	Retrospective
Setting	5 hospitals	3 hospitals	>150 hospitals
Geography	MI, OH, FL, IL	MI, FL	National
Population	Age (60 years) (median) Male (57.5%) Diabetes (40%) Hemodialysis (8%) Charlson score (2) (median) Antibiotics in prior 90d (30%)	Age (59 years) (median) Male (56%) Diabetes (37%) Hemodialysis (21%) Charlson score (3) (median)	Age (61 years) (median) Male (97%) Diabetes (56%) Hemodialysis (2%) Charlson score (6) (median) Antibiotics in prior 90d (87%)
Infections	Various infections	MRSA bloodstream infections	Various infections
Ceftaroline strategy	≥72 hours of ceftaroline	≥72 hours of ceftaroline	≥1 dose of ceftaroline
Time to ceftaroline, median	3 days	NR	3 days
Clinical success, %	88%	68%	NR
Hospital LOS, median	12 days	12 days	5 days
In-hospital mortality, %	8%	22%	5%
30-day hospital readmission, %	9%	NR	33%

NR: not reported