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Adverse drug reactions associated with ceftaroline use: A two-center retrospective cohort

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Abstract

Background—Ceftaroline fosamil is a cephalosporin approved for treating skin and soft tissue infections (SSTIs), including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and community acquired pneumonia (CAP).

Objective—We aimed to study ceftaroline use and associated adverse drug reactions (ADRs), including hypersensitivity reactions (HSRs), among inpatients.

Methods—We performed a retrospective electronic health record review of inpatients from Massachusetts General Hospital and Brigham and Women's Hospital who received ceftaroline between May 2012 and February 2015. ADRs diagnosed by clinical providers during the course of clinical care were subsequently verified and classified. Risk factors for ADRs were identified.

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Results—Among 96 patients (median age 57 years, 54% female) who received a median of 28 [IQR 6, 63] ceftaroline doses, 54% were being treated for MRSA and treatment indications other than SSTI and CAP comprised 59% of care. There were 31 ADRs observed in 20 (21%) of patients; hematologic (n=15) and cutaneous (n=9) findings were most common. Observed HSRs included rash with mucosal lesions (n=1), rash with skin desquamation (n=1) and possible organ specific HSRs (n=2). Patients who suffered an ADR received more doses of ceftaroline (median 46 vs. 21, p=0.013). There was no increased risk of ceftaroline ADR among patients with prior reported beta-lactam allergy (p >0.5).

Conclusions—Ceftaroline is used to treat a range of infections beyond SSTI and CAP. We observed a high rate of ADRs from ceftaroline, including signs of severe HSRs. More data are needed to understand the frequency and predictors of ceftaroline ADRs and HSRs.

Keywords

ceftaroline; adverse drug reaction; hypersensitivity; allergy; beta-lactam; drug

Introduction

Ceftaroline fosamil, a "5th generation" cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA), was approved in the U.S. in 2010 for treatment of complicated skin and soft tissue infections (SSTIs) and community acquired pneumonia (CAP).[1,2] In addition to MRSA, ceftaroline is active against methicillin-susceptible *Staphylococcus aureus* (MSSA), penicillin-resistant *Streptococcus pneumoniae*, and *Haemophilus influenza.*[1,2] Given its strong affinity for Penicillin Binding Protein 2a, its use in the treatment of MRSA infections beyond SSTIs and CAP has expanded beyond its original indications.[3–6] Since the introduction of ceftaroline to the U.S. market in March 2011, it has been used in over 5,500 hospitals and prescribed to over 200,000 patients (L. DiPompo, Pharm.D, Actavis Incorporated, personal communication to J.L.K., May 2015).

Adverse drug reactions (ADRs) occur in 10–15% of inpatients;[7] with drug hypersensitivity reactions (HSRs) comprising about one fifth of all ADRs.[8] ADRs from cephalosporins are uncommon, occurring in 0.0001% to 3% of administrations.[9,10] Although the most common cephalosporin HSR is maculopapular rash, severe HSRs, including anaphylaxis, acute interstitial nephritis (AIN), Stevens-Johnson syndrome (SJS), and Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome have also been described in association with cephalosporin antibiotics.[10,11] In premarketing studies of ceftaroline, ADRs occurred in no greater than 5% of patients.[4,12–15]

There are limited post-marketing data of ceftaroline, and therefore limited experience with ceftaroline ADRs and HSRs. However, some reports suggest that ceftaroline may be associated with more ADRs than identified in premarketing studies.[16–22] Previously reported ceftaroline ADRs include neutropenia, thrombocytopenia, anemia, rashes, eosinophilic pneumonia, and AIN.[16–19,21,22] We aimed to retrospectively describe ceftaroline's pattern of use and resultant ADRs and HSRs in two large academic hospitals.

Methods

We retrospectively identified all patients admitted to either Massachusetts General Hospital (MGH) or Brigham and Women's Hospital (BWH) who received at least one dose of ceftaroline between May 2012 and February 2015 using computerized pharmacy dispensing records. All patients' electronic health records (EHRs) were manually reviewed by two board-certified internists and allergist/immunologists (K.G.B. and J.L.K.).

MGH and BWH, both located in Boston, are tertiary care academic teaching hospitals and founding members of Partners HealthCare, a not-for-profit health care system in Massachusetts. MGH has 999 beds and approximately 48,000 annual admissions; BWH has 793 beds and approximately 46,000 annual admissions. Due to its broad-spectrum activity, as well as cost considerations, ceftaroline use is restricted by each institution's Antimicrobial Stewardship Program through prior authorization. Prior to pharmacy order verification and dispensing of ceftaroline to hospital floors, a physician with specific infectious diseases (ID) privileges must approve its use. The only exception to this policy is during the 8pm–8am time period where a single dose of the drug may be dispensed without ID approval, though approval is required the following day to continue the drug. Both MGH and BWH have inpatient Allergy/Immunology (AI) consultation services that can perform skin testing, test doses/graded challenges, and desensitizations. Both hospitals require allergy consultation for desensitization. Since April 2013, MGH has not required allergy consultation prior to beta-lactam antibiotic test doses (including ceftaroline) because of an inpatient standardized guideline.[23]

Patient age, gender, and self-reported race were determined directly from EHR demographic tables. Comorbidities were determined from the patient's EHR problem list and review of hospital notes. Number of doses and days of ceftaroline therapy were determined based on pharmacy administration data. Concomitant or sequential antibiotic use was defined as exposure to another antibiotic within 24 hours (before or after) of ceftaroline administration, based on the electronic medication administration record. Infections were identified by review of clinical notes. We considered SSTI and CAP as on-label uses for ceftaroline, with other uses off-label. Culture data were obtained from the microbiology record, with predominant organism either the only organism identified or the organism identified with most colonies using standard microbiology descriptors (e.g., abundant, rare). Drug allergy history, including the reported reaction, was collected from the Partners Enterprise Allergy Repository, the centralized electronic allergy repository that stores allergy history throughout Partners HealthCare.[24]

ADRs were initially identified by notes of clinical providers caring for those patients. Only ADRs attributed to ceftaroline by patients' clinical providers were considered for inclusion. For each ADR, we identified the clinical provider(s) who made the ADR diagnosis (e.g., Internal Medicine, AI, ID, etc.). We used the physical exam section of notes to define rashes. Abnormal laboratory findings were verified and included transaminitis (alanine aminotransferase > 100U/L), acute kidney injury (two fold increase in the serum creatinine or 50% decrease in glomerular filtration rate), leukopenia (white blood cell count < 4,000/μL), neutropenia (absolute neutrophil count <1,500/μL), eosinophilia (absolute eosinophil

count ≥500/L), thrombocytopenia (platelet count <150,000U/μL), and fever (temperature ≥100.4 degrees Fahrenheit). Given that all patients had active infections, fever was not considered an ADR/HSR unless there was another sign or symptom of an ADR. Final inclusion of ADRs required the consensus of all AI and ID-trained clinician investigators.

We grouped patients who experienced a single sign or symptom of an ADR and those who experienced more than one sign or symptoms of an ADR. ADRs were classified as possibly immune-mediated or side effect, the latter including both intolerance and toxicity.

For patients with prior reported beta-lactam allergy, we defined identified their specific allergy history, including identification of culprit drug(s), reported reactions, classification of reported allergy, method of initial ceftaroline administration (full dose, test dose, or desensitization), total doses of ceftaroline administered, and outcome. For ADRs to ceftaroline among patients with prior reported beta-lactam allergy, we determined if the ADRs were possibly related to the allergy history.

Descriptive data are displayed as frequencies or medians with interquartile ranges, where appropriate. Comparison of variables between patients who did, and did not, develop an ADR was performed by the Wilcoxon rank sum test for continuous data and the Fisher's Exact test for binary data. Statistical tests were performed in SAS 9.4 (Cary, NC). This study was approved by the Institutional Review Board of Partners Human Research Committee.

Results

Cohort Characteristics

From May 2012 to February 2015, there were 96 patients (median age 57 years, 54% female) who received one or more doses of ceftaroline (Table 1). Common comorbid medical illnesses included hypertension (52%), diabetes (33%), coronary or peripheral vascular disease (28%), chronic kidney disease (24%), intravenous drug use (18%), and atopy (13%). A prior history of drug allergy was observed in 66% of patients. Patients received a median of 28 doses [IQR 6, 63] of ceftaroline over a median of 13 days [IQR 4, 30]. Concomitant or sequential therapy with daptomycin (14%), vancomycin (10%), and other antimicrobials (44%) was observed. Infectious diagnoses included bacteremia (35%), orthopedic infections (28%), SSTI (28%), pneumonia/empyema (22%), and endocarditis (15%). In total, 57 patients (59%) were treated with ceftaroline for an off-label indication. MRSA was the predominant organism identified in patient cultures (54%).

Adverse Drug Reactions

Of the 96 patients, there were 31 ADRS observed in 20 (21%) of patients (Table 2). While 12 patients had a single sign or symptoms of an ADR, 8 patients experienced more than one sign or symptom of an ADR. All but one patient (19/20, 95%) had ADRs that were possibly immune-mediated. ADRs included hematologic abnormalities (n=15), rash (n=9), fever (n=3), acute kidney injury (n=2), transaminitis (n=1), gastrointestinal upset(n=1), and *Clostridium difficile* infection (n=1). Hematologic abnormalities included leukopenia (n=4), neutropenia (n=5), eosinophilia (n=3) and thrombocytopenia (n=3). Rashes were most commonly maculopapular (n=4), but urticaria (n=1) and rashes with involvement of mucosal

lesions (n=1) and skin desquamation (n=1) were also identified. Two rashes were not further characterized. One patient (number 43) was considered to have an immune hepatitis because of transaminitis with concurrent rash. One patient with acute kidney injury (number 81) was considered to have AIN, diagnosed by nephrology consultation after examination of the urinary sediment.

In univariable analyses, the median age of patients who experienced ceftaroline ADRs was younger than patients who did not experience an ADR (median 39 years vs. 60 years, p=0.05). The median number of doses of ceftaroline received by patients who had an ADR was significantly greater compared to those who did not experience an ADR (46 doses vs. 21 doses, p=0.01, Table 3). Patients whose primary reason for ceftaroline use was off-label more frequently experienced an ADR than patients treated with ceftaroline for approved indications (75% vs. 55%, p=0.13).

Patients with drug allergy histories, including patients with any drug allergy history, allergy to penicillin, and allergy to cephalosporins were not more likely to suffer a ceftaroline ADR than those without drug allergy histories (p>0.5, Table 3). Among 25 patients with reported beta-lactam allergy who received at least one dose of ceftaroline, 12 (48%) patients had reported penicillin allergy only, four (16%) patients had reported cephalosporin allergy only, and nine patients (36%) reported allergy to both antibiotic classes. Penicillin allergy histories included anaphylaxis (n=5), swelling (n=1), urticaria (n=3), rash (n=7), hepatitis (n=1), itching (n=1), and unknown (n=3). Cephalosporin allergy histories included anaphylaxis (n=1), urticaria (n=4), rash (n=4), maculopapular rash with eosinophilia, tongue swelling (n=1), and leukocytoclastic vasculitis (n=1). The specific cephalosporin that caused prior allergy was known in 10 patients, and included first (cephalexin and cefazolin), second (cefaclor), third (ceftriaxone and ceftazidime), and fourth (cefepime) generation cephalosporins.

Patients with reported beta-lactam allergy received a median of 22 [IQR, 6–59] doses of ceftaroline. Three patients (patients 9, 74, and 80) received their first dose of ceftaroline by an empiric desensitization procedure due to their prior beta-lactam allergy history. The remaining patients either received ceftaroline at full dose, or initiated therapy with an observed test dose. No patients received skin testing prior to administration.

Excluding the patients desensitized to ceftaroline (n=3), 19/22 (86%) of patients with prior beta-lactam allergy received ceftaroline without any manifestations of an ADR and 21/22 (95%) of patients with prior beta-lactam allergy received ceftaroline without any manifestations of an HSR. Only one patient had a ceftaroline HSR (rash) that was potentially related to their allergy history of urticaria to cefepime. Patients given ceftaroline without ADR/HSR included 4 patients (patients 56, 69, 76, and 50) with prior HSRs that were possibly severe, IgE-mediated HSRs. These patients received between 2 and 114 doses of ceftaroline without complication.

Discussion

We reviewed all ceftaroline use at two academic hospitals, over a nearly three year study period and found that among 96 patients, a majority were treated for MRSA and off-label indications including bacteremia, orthopedic infections, and endocarditis. Ceftaroline was associated overall with a high rate of ADRs. Patients additionally experienced signs of HSRs that are usually rare and severe. This analysis provides insight into the expanded clinical use of ceftaroline and associated ADRs and HSRs.

The rate of ADRs in patients receiving ceftaroline was 21% in our study, substantially higher than the 5–7.5% reported in premarketing studies of ceftaroline, and higher than reported in the largest case series to date (8%).[4,6] The majority of ADRs identified were possibly immune-mediated, and many patients (40%) had more than one manifestation of ADR. Compared to premarketing data, we observed higher rates of eosinophilia, thrombocytopenia, neutropenia, and rash.[4,12–15] The higher incidence of observed ADRs/HSRs is an important finding and of clinical consequence to providers making treatment decisions. While our findings may be partially explained by a patient population who is medically complex with prolonged antibiotic exposures, this is an area that warrants careful future study to understand if the drug has a different propensity to cause ADRs/HSRs than other cephalosporin class antibiotics, or if the observed differences are due to patients factors (i.e., confounding by indication).[9,25,26] Indeed, in the one report that included patients similar to ours (i.e., comorbid patients, long duration of therapy, off-label indications), among 12 inpatients treated with ceftaroline, 9 patients (75%) discontinued ceftaroline because of an ADR.[22] Reported ADRs similarly included cutaneous and hematologic findings.

Prior reports of ADRs to ceftaroline do not contain detailed descriptions of rashes. In contrast, this study identified descriptions of rashes in all but two cases and identified patients who experienced signs of what are usually extremely rare –and often severe— HSRs. In a cohort of less than 100 patients, we observed possible SJS (patient 1) and possible immune-mediated organ specific reactions (patients 43 and 81). Additionally, one rash was described to include skin desquamation, which can be observed with exfoliative dermatitis, as well as other HSRs including a resolving maculopapular rash. More detailed, prospective data collection on patients suffering ceftaroline-related HSRs are crucial to accurately classify HSRs and define the true population risk.

The observed ceftaroline ADR rate in this study is higher than reported ADRs reported generally from the cephalosporin class of antibiotics.[10] However, this difference is not surprising given that the patient population receiving ceftaroline in this study was markedly different than those generally receiving cephalosporins in the literature; the patients in this cohort have substantial infectious burdens with virulent organisms in addition to baseline high medical comorbidities. Compared to our cohort, most data on cephalosporin ADRs and allergic reactions come from mixed inpatient and outpatient samples taking both oral and parenteral cephalosporins. Specifically, in a large and recent retrospective cohort analysis of patients treated with cephalosporins,[10] Our patients were exposed to substantially more doses of drug (mean 43 vs. 1.7 doses), and risk of ADRs is more likely with more doses.

Additionally, our cohort had a high prevalence of reported drug allergy (66%), and patients with any drug allergy history are more likely to have new ADRs and HSRs.[27,28] Interestingly, although our observed ceftaroline ADR rate was high, and higher than most prior data on ceftaroline and cephalosporins, it is actually similar to the rate of ADRs observed with common ceftaroline alternatives, such as vancomycin and linezolid.[29]

Similar to other cephalosporins, ceftaroline's package insert warns that it should not be used in patients with penicillin allergy,[4] and patients with beta-lactam allergies were not part of the early studies of ceftaroline.[12–15] To date, there are few reported cases where a patient with prior beta-lactam allergy received ceftaroline,[2026] and these used empiric desensitizations. Our cohort included 22 patients who received ceftaroline without empiric desensitization, and only one associated HSR (rash in patient 14). This is not surprising given the low likelihood that a patient reporting a beta-lactam allergy is truly allergic,[29] and the low likelihood of cross reactivity between penicillins and cephalosporins.[26,30] Except in cases in which the cephalosporin allergy is to a cephalosporin which shares similar side chains (e.g. ceftobiprole medocaril) or in cases where there is a history of a severe delayed reaction such as SJS/TEN or DRESS syndrome that warrants additional caution,[26,30] patients with penicillin or cephalosporin allergy should largely be able to tolerate ceftaroline. The 22 patients with prior beta-lactam allergy given ceftaroline without desensitization included four patients whose allergy history was suggestive of a severe IgE-mediated HSR. More comprehensive studies are required to determine how ceftaroline should be administered to inpatients with prior penicillin and cephalosporin allergies.[11]

The limitations of our study include those inherent with all retrospective health record reviews, such as incomplete or missing patient information. This is most apparent when trying to categorize HSRs retrospectively. "Rash" was the most specific reaction descriptor in two cases. Even when there were more available details, a complete clinical picture of HSRs were not available. For example, a skin biopsy (patients 1 and 73), a renal biopsy (patient 81), and liver biospy (patient 43) were not performed because they were not needed to inform patient clinical care. Although we used stringent rules for ADR diagnosis and attribution, using assessment by patients' clinical providers, often subspecialists, as well as plausibility assessment by investigators from AI and ID, we were unable to use standardized ADR scores such as the Naranjo or World Health Organization algorithms.[31] We were also limited by the small cohort size and numerically low ADR events (n=20), which led to comprehensively assess ADR risk factors through controlling for confounders in a multivariable analysis. Lastly, the demographic distribution and comorbid illnesses of our urban, referral patient population may not be generalizable to the medical community at large in the U.S., especially since ceftaroline is an Antimicrobial Stewardship Program-restricted antibiotic at both MGH and BWH; hospitals with different stewardship practices may observe different outcomes.

In conclusion, ceftaroline's use has expanded well-beyond its approved indications. In our review, the ADR rate was higher than prior reports, and included patients with signs of HSRs that are usually rare and severe.

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Abbreviations

MRSA	Methicillin-resistant *Staphylococcus aureus*
SSTIs	skin and soft tissue infections
CAP	community acquired pneumonia
MSSA	Methicillin-sensitive *Staphylococcus aureus*
ADR	adverse drug reaction
HSR	hypersensitivity reaction
AIN	acute interstitial nephritis
SJS	Stevens-Johnson syndrome
DRESS	Drug Rash Eosinophilia and Systemic Symptoms
MGH	Massachusetts General Hospital
BWH	Brigham and Women’s Hospital
EHR	electronic health records
ID	Infectious disease
AI	Allergy/Immunology

References

1. Duplessis C, Crum-Cianflone N. Ceftaroline: A New Cephalosporin with Activity against Methicillin-Resistant Staphylococcus aureus (MRSA). Clinical medicine reviews in therapeutics. 2011; 02:3.
2. File TM, Wilcox MH, Stein GE. Summary of ceftaroline fosamil clinical trial studies and clinical safety. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012; 55(Suppl 3):S173–80. [PubMed: 22903949]
3. Pasquale TR, Tan MJ, Trienski TL, File TM Jr. Methicillin-resistant Staphylococcus aureus nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients. J Chemother. 2013 Dec.
4. Laboratories F. TEFLAROÂ® (ceftaroline fosamil) injection for intravenous (IV) use. 2010:22–22.
5. Stryjewski ME, Jones RN, Corey GR. Ceftaroline: clinical and microbiology experience with focus on methicillin-resistant Staphylococcus aureus after regulatory approval in the USA. Diagn Microbiol Infect Dis. 2014; 1281(3):183–8. [PubMed: 25583130]
6. Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother. 2014; 0558(5):2541–6. [PubMed: 24550331]

7. Thong BY, Tan T. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol. 2011; 0571(5):684–700. [PubMed: 21480948]
8. Kelly WN. Potential risks and prevention, Part 1: Fatal adverse drug events. Am J Health Syst Pharm. 2001; 58(14):1317–1324. [PubMed: 11471479]
9. Kelkar PS, Li JT. Cephalosporin allergy. N Engl J Med. 2001; 09345(11):804–9. [PubMed: 11556301]
10. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: A retrospective population-based analysis. J Allergy Clin Immunol. 2015; 135(3):745–52. [PubMed: 25262461]
11. Weiss ME, Bernstein DI, Blessing-moore J, Cox L, Lang DM, Nicklas RA, et al. Drug allergy: An updated practice parameter. Annals of Allergy, Asthma and Immunology. 2010; 105(4):259–273. e78.
12. Corey GR, Wilcox MH, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother. 2010; 65(Suppl 4):iv41–v51. [PubMed: 21115454]
13. Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother. 2010; 65(Suppl 4):iv53–iv65. [PubMed: 21115455]
14. File TM, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. FOCUS 1: A randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother. 2011; 66:491–498.
15. Low DE, File TM, Eckburg PB, Talbot GH, Friedland DH, Lee J, et al. FOCUS 2: A randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother. 2011; 66(Suppl 3):iii33–iii44. [PubMed: 21482568]
16. Griffiths CL, Gutierrez KC, Pitt RD, Lovell RD. Eosinophilic pneumonia induced by ceftaroline. Am J Health Syst Pharm. 2014; 71(5):403–6. [PubMed: 24534595]
17. Rimawi RH, Frenkel a, Cook PP. Ceftaroline - a cause for neutropenia. J Clin Pharm Ther. 2013; 38(4):330–2. [PubMed: 23590618]
18. Sulaiman K, Locati J, Sidhu I, Sangha B. Allergic interstitial nephritis due to ceftaroline. Am J Med Sci. 2014; 348(4):354–5. [PubMed: 25192358]
19. Yam KF, Kwan KB. A case of profound neutropenia and agranulocytosis associated with off-label use of ceftaroline. American Journal of Health-System Pharmacy. 2014; 71(17):1457–1461. [PubMed: 25147169]
20. Jones JM, Richter LM, Alonto A, Leedahl DD. Desensitization to ceftaroline in a patient with multiple medication hypersensitivity reactions. Am J Health Syst Pharm. 2015; 0272(3):198–202. [PubMed: 25596602]
21. Valour F. Does prolonged ceftaroline therapy frequently cause neutropenia? Med Mal Infect. 2014; 44(10):488–488. [PubMed: 25590091]
22. Jain R, Chan JD, Rogers L, Dellit TH, Lynch JB, Pottinger PS. High incidence of discontinuations due to adverse events in patients treated with ceftaroline. Pharmacotherapy. 2014; 34(7):758–63. [PubMed: 24807197]
23. Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol. 2015; (115):294–300. [PubMed: 26070805]
24. Kuperman, GJ.; Marston, E.; Paterno, M.; Rogala, J.; Plaks, N.; Hanson, C., et al. Creating an enterprise-wide allergy repository at Partners HealthCare System. AMIA ...Annual Symposium proceedings / AMIA Symposium. AMIA Symposium; 2003. p. 376-380.
25. Romano A, Torres MJ, Namour F, Mayorga C, Artesani MC, Venuti A, et al. Immediate hypersensitivity to cephalosporins. Allergy. 2002; 57(Suppl 7):52–7. [PubMed: 12144556]

26. Blumenthal KG, Youngster I, Rabideau DJ, Parker RA, Manning KS, Walensky RP, et al. Peripheral blood eosinophilia and hypersensitivity reactions among patients receiving outpatient parenteral antibiotics. J Allergy Clin Immunol. 2015; 136(5):1288–1284. [PubMed: 25981739]

27. Macy E, Ho N. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. Ann Allergy Asthma Immunol. 2012; (108):88–93. [PubMed: 22289726]

28. Solensky R, Khan D. Drug allergy: An updated practice parameter. Annals of Allergy, Asthma and Immunology. 2010; (105):259–73.

29. An MM, Shen H, Zhang JD, Xu GT, Jiang YY. Linezolid versus vancomycin for meticillin-resistant Staphylococcus aureus infection: A meta-analysis of randomised controlled trials. Int J Antimicrob Agents. 2013; 41(5):426–433. [PubMed: 23537580]

30. Talbot GH, Thye D, Das A, Ge Y. Phase 2 study of ceftaroline versus standard therapy in treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother. 2007; 51(10): 3612–3616. [PubMed: 17682094]

31. Berry LL, Segal R, Sherrin TP, Fudge KA. Sensitivity and specificity of three methods of detecting adverse drug reactions. Am J Hosp Pharm. 1988; 45(7):1534–1539. [PubMed: 3046347]

HIGHLIGHTS

1. What is already known?

Ceftaroline is a "5th generation" cephalosporin that treats methicillin-resistant *Staphylococcus aureus* (MRSA). While cephalosporin class antibiotics infrequently cause adverse drug reactions (ADRs) (<2%, with hypersensitivity reactions [HSRs] <0.5%), there are limited available data on ceftaroline.

2. What does this article add to our knowledge?

We identified 96 inpatients treated with ceftaroline. Twenty patients (21%) suffered an ADR, more common than identified in pre-marketing studies. ADRs included HSRs that were suggestive of severe HSRs, including rash with mucosal lesions (n=1), rash with skin desquamation (n=1), and possible organ specific HSRs (n=2).

3. How does this study impact current management guidelines?

Ceftaroline may result in more ADRs, including HSRs, than premarketing data identified. The observed discrepancy may be related to ceftaroline's use for expanded indications in a population with more comorbid conditions, prior drug allergy, and longer treatment duration. Larger, detailed cohorts of patients on ceftaroline are needed to fully understand ADR and HSR risk.

Table 1

Patient Demographics and Antimicrobial Exposure (n=96)

Patient Characteristics	
Median age, IQR	57 [37, 70]
Female Sex (n, %)	52 (54)
Race (n, %)	
White	88 (92)
African American	3 (3)
Hispanic	3 (3)
Other/Unknown	2 (2)
Comorbidities (n, %)	
Hypertension	50 (52)
Diabetes Mellitus	32 (33)
Coronary or peripheral vascular disease	27 (28)
Chronic kidney disease	23 (24)
Intravenous drug use	17 (18)
Atopy	12 (13)
Hepatitis C infection	11 (11)
HIV infection	4 (4)
Any drug allergy history	63 (66)
Penicillin allergy history	20 (21)
Cephalosporin allergy history	13 (14)
Treatment Characteristics	
Doses of ceftaroline, Median [IQR]	28 [6–63]
Days of ceftaroline, Median [IQR]	13 [4–30]
Concomitant or sequential antibiotic use (n, %)	
Daptomycin	14 (14)
Vancomycin	10 (10)
Rifampin	6 (6)
Linezolid	5 (5)
Other *	43 (44)
Infectious Diagnosis (n, %) †	
Bacteremia	34 (35)
Orthopedic infections ‡	27 (28)
Skin/soft tissue infections	27 (28)
Pneumonia/empyema	21 (22)
Endocarditis	14 (15)
Vascular graft infection	8 (8)
Intra-abdominal infections	2 (2)
Epidural abscess	1 (1)
Patients Treated Off-Label	57 (59)

Patient Characteristics	
Organism (n, %)	
MRSA	52 (54)
CoNS	10 (10)
MSSA	5 (5)
Other [//]	9 (9)
Not identified or recovered	20 (21)

[*] Other includes azithromycin, cefazolin, cefepime, ceftazidine, ciprofloxacin, clindamycin, colistin, doxycycline, fluconazole, imipenem, inhaled tobramycin, levofloxacin, meropenem, metronidazole, micafungin, moxifloxacin, nafcillin, piperacillin-tazobactam, and trimethroprim-sulfamethoxazole.

[†] Of the patients with a primary infectious diagnosis of bacteremia some patients also had a secondary diagnosis of endocarditis (n=2), intra-abdominal infection (n=2), pneumonia (n=1); of the with primary orthopedic infections some patients also had a secondary diagnosis of bacteremia (n=8); of the patients with a primary diagnosis of skin and soft tissue infection some patients also had a secondary diagnosis of bacteremia (n=2), pneumonia (n=1), orthopedic (n=2); of the patients with a primary infectious diagnosis of pneumonia some patients also had a secondary diagnosis of bacteremia (n=2); of the patients with a primary diagnosis of endocarditis some patients also had a secondary diagnosis of bacteremia (n=5), pneumonia (n=4), vascular (n=1); of the patients with a primary diagnosis of vascular infection some patients also had a secondary diagnosis of bacteremia (n=2), pneumonia (n=1)

[‡] Orthopedic infections include osteomyelitis, prosthetic joint infections, septic arthritis, post-operative spine infections, and infections after fracture/fixation

[//] Includes *Pseudomonas aeruginosa* (n=2), *Enterobacter aerogenes* (n=1), *Klebsiella pneumoniae* (n=1), Candida albicans (n=1), *Enterococcus faecalis* (n=1), *Staphylococcus lugdunensis* (n=1), Beta-hemolytic Streptococcus (n=1), *Streptococcus pneumoniae* (n=1)

Abbreviations: HIV: Human Immunodeficiency Virus, MRSA: Methicillin-resistant *Staphylococcus aureus*, CoNS: Coagulase-negative *Staphylococcus*, MRSA: Methicillin-sensitive *Staphylococcus aureus*

Table 2

Adverse Drug Reactions to Ceftaroline (n=20)

	Patient number	Ceftaroline doses prior to ADR	Clinical Diagnosis Made by*	Rash†	Transaminitis (Maximum ALT)	Acute kidney injury (Maximum Cr)	Leukopenia (MinimumWBC)	Neutropenia (Minimum ANC)	Eosinophilia (Maximum AEC)	Thrombocytopenia (Minimum PLT)	Fever	*C.difficile*	Gastrointestinal Upset
Two or more signs orsymptoms of ADR	1	76	ID	MUC	...	...	...	1,260	750	...	...	...	...
	24	46	ID	...	...	...	...	270	...	...	X	...	X
	27	40	ID, H	MP	...	...	1,930	...	...	...	X	...	...
	28	129	ID	...	...	...	3,500	...	...	139,000	...	...	...
	40≠	79	ID	...	...	...	...	1,440	...	...	X	...	...
	43	180	ID	MP	369U/L//	...	...	...	...	...	...	...	...
	73	24	AI, ID, D	DES	...	...	2,100	...	910	...	...	...	...
	95	192	ID	...	...	...	3,200	...	760	...	...	...	...
Single sign or symptom of ADR	14≠	4	ID	NC	...	...	...	...	...	...	...	...	...
	15	94	ID	...	...	...	...	...	...	...	...	X	...
	16	40	ID	...	...	...	...	...	...	71,000	...	...	...
	18	18	ID	MP	...	...	...	...	...	...	...	...	...
	29	114	IM	NC	...	...	...	...	...	...	...	...	...
	31	132	ID, H	...	...	...	...	200	...	...	...	...	...
	48	24	ID	MP	...	...	...	...	...	...	...	...	...
	53	46	ID	...	...	...	...	1,400	...	...	...	...	...
	62	15	ID, AI	URT	...	...	...	...	...	...	...	...	...
	76≠	6	IM, H	...	...	...	...	...	...	32,000	...	...	...
	81	48	ID, N	...	...	2.61 (BL 0.60)§	...	...	...	...	...	...	...
	88	22	ID, N	...	...	1.19 (BL 0.66)	...	...	...	...	...	...	...
				Possibly Immune-Mediated HSR								Side effect	

*ID: Infectious Disease, H: Hematology, AI: Allergy/Immunology, D: Dermatology, IM: Internal Medicine, N: Nephrology

†MUC: with mucosal lesions; MP: maculopapular; DES: desquamating; NC: not characterized; URT: urticarial

≠Patients with prior reported history of beta-lactam allergy.

‖Suspected immune-mediated hepatitis

§Suspected acute interstitial nephritis

Abbreviations: ADR: adverse drug reaction, ALT: alanine aminotransferase (U/L), Cr: creatinine (mg/dL), WBC: white blood cell count (U/μL), ANC: absolute neutrophil count (U/μL), AEC: absolute eosinophil count (U/L), PLT: platelet count (U/μL), GI: gastrointestinal, BL: baseline, HSR: hypersensitivity reaction.

Table 3

Predictors of Adverse Drug Reactions Among Patients Receiving Ceftaroline (n=96)

Patient Characteristics	**ADR (n=20)**	**No ADR (n=76)**	**P value***
Age, Med [IQR]	39 [32,65]	60 [42,71]	0.05
Female Sex, n (%)	12 (60)	40 (53)	0.62
White Race, n (%)	19 (95)	69 (91)	0.65
Comorbidities, n (%)			
Atopy	2 (10)	10 (13)	1.00
Hypertension	7 (35)	43 (57)	0.13
Diabetes Mellitus	9 (45)	23 (30)	0.29
Coronary or peripheral vascular disease	3 (15)	24 (32)	0.17
Chronic Kidney Disease,	2 (10)	18 (24)	0.23
Hepatitis C Infection	0 (0)	11 (15)	0.11
HIV Infection	0 (0)	4 (5)	0.58
Intravenous Drug Use	5 (25)	12 (16)	0.34
Any drug allergy	12 (60)	51 (67)	0.60
Penicillin allergy	3 (15)	17 (23)	0.55
Cephalosporin allergy	2 (10)	11 (15)	1.00
Treatment Characteristics			
Doses of ceftaroline, Med [IQR]	46 [21, 104]	21 [6, 59]	0.01
Off label indications, n (%)	15 (75)	42 (55)	0.13

*Wilcoxan rank sum test for continuous variables and Fisher's Exact for binary variables