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ORIGINAL RESEARCH ARTICLE

Retrospective Cohort Evaluating the Comparative Effectiveness of Ceftaroline and Daptomycin as First-Line Therapies for Inpatient Treatment of Diabetic Foot Infection in the United States Veterans Health Care System

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Abstract

Background Both ceftaroline and daptomycin are possible therapeutic options for diabetic foot infection (DFI) and both are active against methicillin-resistant *Staphylococcus aureus* (MRSA) infection; however, no previous studies have evaluated their effectiveness head-to-head.

Objective This study compared hospital readmission and mortality proportions among patients receiving ceftaroline fosamil or daptomycin for DFI.

Patients and Methods This was a retrospective cohort, comparative effectiveness study of adults (aged ≥ 18 years) admitted to United States Veterans Health Care System hospitals with a diagnosis code for DFI between 1 October 2010 and 30 September 2014 with an electronic order for ceftaroline or daptomycin as first-line therapy within 14 days of admission. Baseline characteristics were compared using Chi-square, Fisher's exact, and Wilcoxon rank-sum tests. Hospital readmission and patient mortality proportions were compared through multivariable logistic regression models with Hispanic ethnicity, prior hospitalization, dyslipidemia, and Charlson comorbidity score as covariates.

Results In total, 223 patients were included (ceftaroline, $n = 71$; daptomycin $n = 152$). At baseline, ceftaroline patients were more likely to be Hispanic (18 vs. 6%, $p < 0.01$) and have been hospitalized in the past 90 days (34 vs. 19%, $p = 0.02$). Unadjusted 90-day hospital readmission proportions for ceftaroline versus daptomycin were 34 vs. 49%, and unadjusted 90-day mortality proportions were 1% vs. 8%. In multivariable models, ceftaroline patients were less likely to experience 90-day hospital readmission (odds ratio [OR] 0.46, 95% confidence interval [CI] 0.25–0.85) and 90-day mortality (OR 0.14, 95% CI 0.01–0.77).

Conclusions In this population, ceftaroline was associated with lower 90-day hospital readmission and 90-day mortality compared with daptomycin when used as first-line therapy for DFI.

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Key Points

This was a retrospective comparative effectiveness study of patients with diabetic foot infections.

Ceftaroline was associated with fewer hospital readmissions compared with daptomycin.

Ceftaroline was associated with lower mortality compared with daptomycin.

1 Introduction

Up to 25% of patients with diabetes will experience a diabetic foot infection (DFI) during their lifetime [1]. DFIs are difficult to treat due to limited antibiotic penetration, frequent polymicrobial infection, and an increased incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Currently, the FDA has indicated only three antibiotics for the treatment of DFIs (piperacillin and tazobactam, ertapenem, and linezolid), but many others are used for treatment off-label [2]. The Infectious Diseases Society of America (IDSA) recommends empiric therapy based on infection severity and any recent microbiological data [2]. Currently, there is not a preferred therapeutic regimen that offers a significant benefit over others [3].

Gram-positive bacteria are the most common infectious organisms and MRSA is implicated in up to 17% of DFIs [4]. Empiric coverage against MRSA requires antimicrobial agents that are both effective for the treatment of DFIs and active against this pathogen. The 2012 IDSA guidelines recommend starting empiric therapy with an anti-MRSA agent in areas of high prevalence, for severe infections, and in patients with a history of MRSA infection or colonization [2]. Vancomycin is considered a mainstay treatment option to empirically cover MRSA, but daptomycin and linezolid are also suggested. For DFIs where polymicrobial infection is not suspected, monotherapy with one of these anti-MRSA agents is recommended. Vancomycin has reported success proportions of 69–73% in treating DFIs, while daptomycin and linezolid show proportions of 66–91% and 76–87%, respectively [5–9].

Ceftaroline was specifically omitted from the 2012 IDSA guidelines since it was approved on the basis of studies that excluded patients with DFIs. Ceftaroline studies in patients with complicated skin and skin structure infections, excluding DFIs, demonstrated success proportions of 92% [10, 11]. Since publication of the 2012 guidelines, ceftaroline has seen more widespread use for off-label treatment of DFIs, and subsequent studies have evaluated ceftaroline's efficacy specifically in this situation. Ceftaroline was found to achieve an overall success proportion of 81% in a retrospective observational study of patients treated for DFIs, including infections involving MRSA [12]. This proportion is comparable with that reported for currently recommended therapies, but no direct head-to-head comparisons between ceftaroline and these therapies for the treatment of DFIs have been performed to date. In addition, no studies to date have evaluated mortality or hospital readmission proportions using ceftaroline to treat DFIs. A direct head-to-head comparison with current treatments and additional outcomes data may provide insight into the suitability of ceftaroline's use for this indication and prompt reconsideration of ceftaroline's place in guideline recommendations.

Both ceftaroline and daptomycin are possible therapeutic options for DFIs and both are active against MRSA; however, no previous studies have evaluated their effectiveness head-to-head. Ceftaroline has added gram-negative coverage compared with daptomycin. This difference could be important from an efficacy standpoint as well as an antimicrobial stewardship standpoint. A direct comparison of clinical outcomes is needed to establish whether ceftaroline is an acceptable recommendation for the empiric treatment of DFIs. This study compared 90-day hospital readmission proportions and mortality proportions for patients with DFIs who received ceftaroline or daptomycin as first-line therapy.

2 Methods

2.1 Data Source

Data were obtained from the Veterans Health Administration (VHA) electronic medical record (EMR), which includes administrative, clinical, laboratory, and pharmacy data. The VHA EMR is linked between all US-based VHA sites. The data compiled for this study thus represent nationwide VHA use of ceftaroline and daptomycin within the study period. The Institutional Review Board of the University of Texas Health Science Center at San Antonio and the South Texas Veterans Health Care System Research and Development Committee approved this study.

2.2 Study Design

This was a retrospective cohort, comparative effectiveness study of adults aged ≥ 18 years in the US VHA with a diagnosis code for DFI during their hospital stay between 1 October 2010 and 30 September 2014.

Variables were determined prior to study initiation and included patient characteristics (age, race, Hispanic ethnicity, comorbidities, prior medications, and concomitant medications), treatment setting, the exposures of interest (ceftaroline and daptomycin use), and treatment outcomes (length of stay, 90-day hospital readmission, and 90-day patient mortality). International Classification of Diseases, Ninth Revision (ICD-9) and Clinical Modification Diagnosis (CSS) codes were utilized to identify patients with DFI and comorbidities (see electronic supplementary material [ESM] 1 and 2).

2.3 Inclusion and Exclusion Criteria

This study was designed to assess the effectiveness of ceftaroline and daptomycin as first-line therapy for patients with DFI. Patients hospitalized within the study period with a diagnosis of DFI and an electronic order for ceftaroline or daptomycin within 14 days of hospital admission were included in the study. Patients with pneumonia were excluded from this study because daptomycin interacts with pulmonary surfactant, rendering it suboptimal for treatment of patients with concomitant pneumonia. Patients who received both drugs were excluded from the study.

2.4 Statistical Analysis

Two-way statistical tests, including the Chi-square, Fisher's exact, Student's *t*, and Wilcoxon rank-sum tests, were used to compare baseline characteristics of patients treated with each agent. Baseline characteristics found to be significantly different ($p \leq 0.05$) with two-way statistical tests were selected as covariates for the multivariable models. Multivariable analyses were conducted to account for the effects of dissimilar baseline characteristics between treatment arms. JMP Pro 12.1.0 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

3 Results

A total of 223 patients met the study criteria (ceftaroline, $n = 71$; daptomycin, $n = 152$). Compared with daptomycin patients, ceftaroline patients were similar in median (interquartile range [IQR]) age [61 years (57–66) vs. 60 years (55–63), $p = 0.23$], were more likely to be Hispanic (18 vs. 6%, $p = 0.0043$), had a higher proportion of prior hospitalizations in the last 90 days (34 vs. 19%, $p = 0.02$), and were more likely to have peptic ulcer disease (6 vs. 1%, $p = 0.02$) [see Table 1 for a full comparison of all baseline characteristics]. Median (IQR) time from admission to drug initiation was 0 (0–1) days for ceftaroline and 1 (0–1) day for daptomycin.

Regarding patient outcomes (Fig. 1), the unadjusted 90-day hospital readmission proportions for ceftaroline and daptomycin were 34 vs. 49% (odds ratio [OR] 0.54, 95% confidence interval [CI] 0.30–0.97; $p = 0.04$). Unadjusted 90-day mortality proportions were 1 vs. 8% (OR 0.17, 95% CI 0.02–1.31; $p = 0.05$). In multivariable models with all divergent baseline characteristics included as covariates (Fig. 2), patients treated with ceftaroline were less likely to experience 90-day hospital readmission (OR 0.46, 95% CI 0.25–0.85) and 90-day mortality (OR 0.14, 95% CI 0.01–0.77) than those treated with daptomycin.

4 Discussion

In this retrospective assessment of outcomes following real-world use of ceftaroline and daptomycin within the VHA for DFI, multivariable models demonstrated fewer hospital readmissions and lower mortality with ceftaroline versus daptomycin.

Daptomycin is a guideline-recommended, empiric treatment option for DFIs with suspected MRSA involvement. To our knowledge, this is the first direct comparison of ceftaroline with another guideline-recommended antibiotic for the treatment of DFIs. The results of this comparison support the use of ceftaroline for this purpose.

As previous studies established, clinical cure proportions of ceftaroline and daptomycin for DFIs were within the same range of each other (81% for ceftaroline, 66–91% for daptomycin) [5–7, 12]. Clinical cure proportions for other guideline-recommended therapies for suspected MRSA involvement were also comparable (69–73% for vancomycin, 71–87% for linezolid) [5, 8, 9]; however, previous studies did not collect data on readmission or mortality proportions. These outcome data are important from an economic and clinical perspective. Hospital reimbursement for Medicare patients depends on readmission proportion, and developing a DFI is a known, independent risk factor for mortality [13].

Currently, readmissions and mortality data for individual antibiotics in the treatment of DFI are widely unavailable. Comparisons with vancomycin and linezolid in these categories are therefore not possible at this time. However, these data for the treatment of DFIs overall have been collected. A single-center study of patients enrolled in a multidisciplinary

Table 1 Baseline characteristics for patients who received first-line ceftaroline and daptomycin for diabetic foot infection

Variables	Ceftaroline [$n = 71$]	Daptomycin [$n = 152$]	p value
Age, years [median (IQR)]	61 (57–66)	60 (55–63)	0.23
Male, %	97	94	0.32
Married, %	41	48	0.16
Race and ethnicity, %			
White, non-Hispanic	63%	74	0.11
Black, non-Hispanic	18	17	0.86
Hispanic	18	6	**< 0.01**
Other, non-Hispanic	0	3	0.17
Missing	0	1	0.33
Charlson comorbidity score [median (IQR)]	7 (4–8)	6 (4–7)	0.26
Comorbidities, %			
Congestive heart failure	31	26	0.41
COPD	35	29	0.35
Cerebrovascular disease	10	14	0.34
Dementia	0	1	0.33
Diabetes (complications)	56	51	0.48
Diabetes (no complications)	100	95	0.07
Hemi/paraplegia	0	1	0.33
HIV	0	1	0.49
AIDS	1	1	0.96
Liver (mild)	4	5	0.90
Liver (mod/severe; cirrhosis)	7	7	0.90
Cancer	10	9	0.75
Leukemia	1	0	0.14
Metastatic cancer	0	1	0.49
Myocardial infarction	4	4	0.92
Peptic ulcer disease	6	1	**0.02**
Peripheral vascular disease	30	27	0.69
Renal disease	42	42	0.98
Rheumatic disease	0	3	0.12
Dyslipidemia	82	70	0.07
Hypertension	92	89	0.63
Hemodialysis	0	2	0.23
Prior hospitalization (past 90 days), %	34	19	**0.02**
Prior antibiotics (past 90 days), %	72	65	0.32
Intensive care unit, %	4	7	0.39
Weight, lbs [median (IQR)]	233 (187–281)	249 (202–287)	0.27

Bold values indicate statistically significant p values ($p < 0.05$)

IQR interquartile range, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *AIDS* acquired immunodeficiency syndrome

diabetic foot service at Johns Hopkins found the overall unplanned 30-day readmission proportions for patients treated for DFI to be 17% [14]. A multicenter study of state inpatient hospitals and emergency departments in Florida and New York found 30-day readmission proportions of 30% [15]. The 90-day readmission proportions in our study of VHA patients were found to be 34% for ceftaroline and 49% for daptomycin. However, different treatment settings, lack of stratification by first-line antibiotic in prior studies, and varying time frames of reported proportions make it impossible to compare the readmission outcomes observed in this study with those of different therapy options identified in previous studies.

In addition to readmission proportions, this study also analyzed 90-day mortality proportions. Developing a DFI is a known, independent risk factor for mortality. The 5-year mortality proportion of patients with diabetic foot

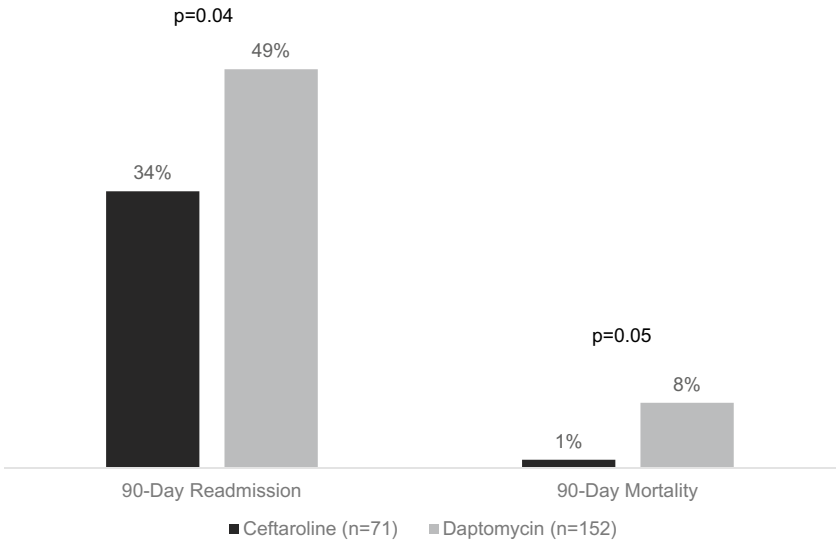

Fig. 1 Unadjusted 90-day hospital readmission proportions and 90-day mortality proportions for patients receiving first-line ceftaroline and daptomycin for diabetic foot infections

ulcers was estimated to be approximately 40%, but proportions could vary from 26 to 63% [16]. Data on 90-day mortality proportions involving DFIs were most often reported for patients who underwent amputation due to more severe infections and underlying disease. These proportions are not directly comparable with those found in our study for antibiotic treatment with ceftaroline or daptomycin. As with readmission outcomes, current literature does not exist to compare mortality outcomes of ceftaroline or daptomycin with other guideline-recommended therapies. While additional data are necessary for a more thorough evaluation of other therapies, this retrospective VHA study has established that first-line ceftaroline exhibited significantly lower 90-day readmission proportions and 90-day mortality proportions compared with first-line daptomycin.

A previous systematic review did not find a significant benefit associated with any single antibiotic agent in the treatment of DFIs [3]. Current IDSA guidelines recommend only three treatments options for DFI with suspected MRSA involvement: vancomycin, linezolid, and daptomycin [2]. Ceftaroline has similar clinical success proportions as all three of these therapies, and significantly lower hospital readmission and mortality proportions than daptomycin [5–7, 12]. These conclusions support the use of ceftaroline fosamil as a first-line antibiotic for the treatment of DFI. Additional factors of safety, cost, and therapeutic burden should be included when considering ceftaroline fosamil for this purpose.

Due to the patient population served by the VHA, there are some limitations regarding external validity. First, 95% of patients included in the study were male. Moreover, baseline characteristics and comorbidities were likely to affect hospital readmission and patient mortality. In this study, patients in each treatment arm were mostly similar in baseline characteristics and comorbidities; however, Hispanic patients were more represented in the ceftaroline treatment arm, and the ceftaroline treatment arm had a higher incidence of baseline peptic ulcer disease and prior hospitalization. To remove confounding, multivariable analyses were performed to account for differences in baseline characteristics and comorbidities. However, we were unable to account for antibiotic timing and antibiotics received prior to hospitalization, and there might be unknown confounders, such as amputation, that affect the measure of association. Due to the misbalance of individuals reporting Hispanic ethnicity between the two exposure groups, there might be an underlying difference as to why providers prescribed one therapy as opposed to the other. Furthermore, it is unknown if differences in dosing frequency, and the associated burden on nursing staff, played a role in drug selection. In addition, readmissions and mortality were all-cause, therefore underlying issues besides just DFI may have led to these negative outcomes. Furthermore, the study has a small sample size and the numbers of patients in each treatment arm were not equal. This was not a direct comparison, as seen in randomized controlled trials. Nevertheless, these real-world data are useful for clinical decision making. Finally, local prescribing patterns and drug availability likely impacted drug selection.

In spite of its limitations, our study also has notable, important strengths. This study has a larger population than previous studies. To date, it is the largest comparative effectiveness study of ceftaroline and daptomycin in the real-world treatment of DFI. The VHA is the largest integrated health care system in the US, with facilities in all 50 states. The VHA EMR data consist of clinical, pharmacy, and administrative data. These repositories are a comprehensive source for evaluating mortality, even when it occurs outside the hospital.

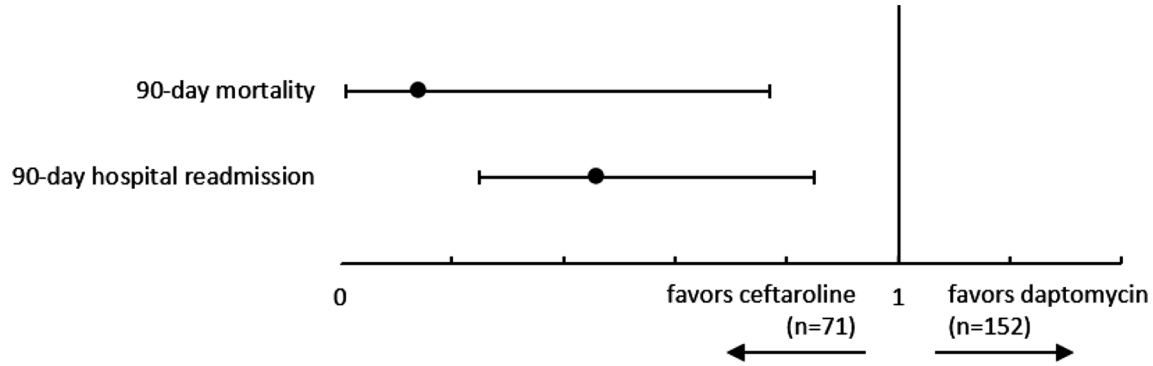

Fig. 2 Adjusted hospital readmission and patient mortality for patients receiving first-line ceftaroline and daptomycin for diabetic foot infections

Further studies are needed with a larger patient population, a greater proportion of female patients, and an equal distribution of ethnic backgrounds. A network meta-analysis could provide additional useful information. Randomized controlled trials can be conducted to reduce bias and confounding factors.

5 Conclusions

This real-world effectiveness study of patients with DFI demonstrates that first-line ceftaroline is associated with lower proportions of 90-day hospital readmission and lower 90-day patient mortality than first-line daptomycin. While this study provided preliminary information on the use of ceftaroline and daptomycin for DFI, these findings must be confirmed or refuted in a larger, more diverse patient population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-022-00319-1.

Declarations

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Conflict of interest This work was supported by TEF-IT-41, an investigator-initiated grant to Dr. Frei's institution, from Actavis Pharmaceuticals (formerly Forest and Allergan Pharmaceuticals). Alyssa C. Eaves, Chengwen Teng, and Kirk E. Evoy declare no potential conflicts of interest or competing interests.

Ethics approval The Institutional Review Board of the University of Texas Health Science Center at San Antonio and the South Texas Veterans Health Care System Research and Development committee approved this study.

Consent to participate Not applicable.

Consent for publication All authors consent to the publication of this manuscript.

Availability of data and material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability The code that supports the findings of this study is available from the corresponding author upon reasonable request.

Author contributions Study concept and design: CRF. Statistical analysis: CRF. Interpretation of data: All authors. Drafting of the manuscript: ACE, CT, KEE, CRF. Critical revision of the manuscript for important intellectual content: All authors. Study supervision: CRF. All authors read and approved of the final version.

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