TITLE PAGE

Title: A Multicenter Observational Study of Ceftaroline Fosamil for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections

Authors: Evan J. Zasowski[1], Trang D. Trinh[1], Kimberly C. Claeys[1,2], Anthony M. Casapao[1,3], Noor Sabagha[1], Abdalhamid M. Lagnf[1], Kenneth P. Klinker[4], Susan L. Davis[1, 5], Michael J. Rybak[1, 6,7]#

[1] Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA

[2] Department of Pharmacy Practice, University of Maryland School of Pharmacy, Baltimore, MD, USA

[3] Department of Pharmacy Practice, Husson University School of Pharmacy, Bangor, ME, USA

[4] University of Florida, College of Pharmacy, Gainesville, FL, USA

[5] Department of Pharmacy Services, Henry Ford Hospital, Detroit, MI, USA

[6] Department of Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit, MI, USA

[7] Department of Pharmacy Services, Detroit Medical Center, Detroit, MI, USA

Key words: MRSA; bacteremia; treatment failure; infective endocarditis; pneumonia; bone and joint infection; beta-lactam; vancomycin; daptomycin

Running title: Ceftaroline fosamil for MRSA bloodstream infections

Corresponding author: Michael J. Rybak, Pharm.D., M.P.H., Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Ave, Detroit, MI 48201, M.Rybak@wayne.edu

ABSTRACT

Novel therapies for methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) are needed in the setting of reduced antibiotic susceptibilities and therapeutic failure. Ceftaroline is an advanced generation cephalosporin with MRSA activity. Although not FDA approved for MRSA BSI, ceftaroline has generated much interest as a potential treatment option. However, detailed description of its use in this setting remains limited. To address this, we conducted a retrospective, multicenter, observational study of adult patients with MRSA BSI treated with at least 72 hours of ceftaroline from 2011 to 2015. Safety outcomes were examined in the overall cohort while efficacy outcomes were examined among patients who had not cleared their BSI prior to ceftaroline initiation. Data were also stratified by ceftaroline monotherapy or combination therapy. Predictors of clinical failure on ceftaroline were also sought. Overall, 211 patients were included in the safety population; *Clostridium difficile* infection, rash, and neutropenia occurred in 6 (2.8%), 7 (3.3%), and 3 (1.4%) of patients, respectively. Clinical success was observed in 86 (68.3%) of the 126 patients included in efficacy population. The monotherapy and combination therapy subgroups had a similar proportion of patients experiencing success (69.7 and 64.9%, respectively). The median BSI duration post-ceftaroline was 2 (1 – 4) days among monotherapy and 3 (1.5 – 5) days for combination therapy. Higher APACHE II score and comorbid malignancy independently predicted treatment failure. Ceftaroline appears effective for MRSA BSI as both monotherapy and combination therapy. However, comparative studies are needed to further delineate the role of ceftaroline in MRSA BSI treatment.

TEXT

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be a tremendous public health issue, causing a range of infections in both community and healthcare settings.(1) It is estimated to result in more than 80,000 invasive infections and 11,000 deaths in the United States annually.(1) Bloodstream infections (BSI) caused by MRSA have been associated with substantial morbidity, mortality, and healthcare costs.(2-4) Although vancomycin is considered the treatment of choice for MRSA BSI, treatment failure, emergence of reduced vancomycin susceptibility phenotypes such as heterogeneous vancomycin-intermediate *Staphylococcus aureus*, and adverse drug reactions necessitate alternative treatment options.(5-7) Daptomycin is currently the primary alternative to vancomycin for MRSA BSI, but its use is not without limitation.(5, 8-11) Interactions with pulmonary surfactant render daptomycin ineffective for BSI secondary to respiratory source.(12) Daptomycin non-susceptible *Staphylococcus aureus* has also emerged along with descriptions of daptomycin failure following vancomycin failure. (13-15) Collectively, the limitations of these two standard of care agents for MRSA BSI demonstrate the urgent need for additional evidence based antibiotic therapies.

Ceftaroline fosamil, the pro-drug of ceftaroline, is an advanced generation cephalosporin with potent bactericidal gram-positive activity.(16) To date, it is the only beta-lactam antibiotic commercially available in the United States with inherent activity against MRSA. Although not FDA labeled for *Staphylococcus aureus* BSI, ceftaroline fosamil, herein ceftaroline, has garnered considerable interest for the treatment of MRSA BSI. (17) However, currently published data examining the effectiveness and safety of ceftaroline specific to MRSA

BSI are limited. Most investigations are limited by small sample size and frequently describe ceftaroline used in combination with other MRSA-active therapies for treatment refractory BSI.(17-24) Therefore, this analysis sought to provide a detailed, multicenter description of the clinical characteristics and outcomes of patients with MRSA BSI treated with ceftaroline, as monotherapy or combination therapy. As a secondary objective, we also sought to explore factors independently associated with clinical failure among patients treated with ceftaroline for MRSA BSI.

MATERIALS AND METHODS

Study Design and Population

This was a retrospective, multicenter observational study conducted between 2011 and 2015 at the Detroit Medical Center, Henry Ford Health System, and University of Florida Health – Shands Hospital. Patients age 18 years and older with at least one positive blood culture for MRSA meeting CDC BSI criteria receiving at least 72 hours of ceftaroline were included.(25) This study was approved by the institutional review board at each institution and waiver of informed consent was granted.

Patient Data Elements and Collection

Eligible subjects were identified through screening a list of all patients receiving ceftaroline at each institution during the study period. Patient data were extracted from the medical record by trained reviewers using a structured data collection form within REDCap (Research Electronic Data Capture, Vanderbilt University), an electronic data capture tool hosted at Wayne State University.(26) Data elements included patient demographics, past

medical history, co-morbid conditions, hospitalizations in the past year, receipt of systemic antibiotics in the past 90 days, surgery, chemotherapy/radiation therapy, or receipt of immunosuppressive medications in the past 30 days. The degree of patient comorbidity was quantified using the Charlson comorbidity index.(27) Severity of illness was quantified using the Acute Physiology and Chronic Health Evaluation (APACHE) II score using the worst parameters within 24 hours of the index MRSA blood culture. (28, 29) The source(s) of MRSA BSI were based on treating physicians' notes and the available clinical and diagnostic data. Microbiologic data including antibiotic susceptibilities by Microscan, Vitek II, BD Phoenix, and/or Etest were collected from the medical record. Polymicrobial BSI was defined as isolation of an additional pathogen satisfying CDC BSI criteria within 24 hours of index MRSA BSI isolate.(25) Treatment data including infectious diseases team consult, source control attempt(s), and antimicrobial treatment data including associated laboratory data were documented. Combination therapy was defined as receipt of concurrent MRSA-active therapy with ceftaroline for ≥ 24 hours.

Outcomes

The primary outcome of interest was clinical success defined as BSI clearance, cessation of BSI signs and symptoms (i.e. fever, leukocytosis) by the end of therapy or discharge (whichever is sooner), and alive at hospital discharge. Patients not classified as success were considered to have experienced treatment failure. Secondary outcomes included all-cause in-hospital mortality, BSI clearance and duration post-ceftaroline initiation, and hospital length of stay post-ceftaroline initiation. Bloodstream infection clearance was defined as a series of two consecutive negative blood cultures, with date of clearance considered the day of the first negative culture. Safety outcomes included specific, *a priori* defined inpatient adverse drug

reactions including rash, *Clostridium difficile*-associated diarrhea, and neutropenia after the first dose of ceftaroline. Neutropenia was objectively defined as a decrease in neutrophil count to < 1,500 cells/mm^3 or > 50% decrease from baseline (first ceftaroline dose) if baseline ≤ 1,500 cells/mm^3 from first dose to 72 hours after last ceftaroline dose.(30)

Data Analysis

Patients were grouped into two populations for data analysis: a safety population consisting of all included patients and an efficacy population consisting of patients who had not cleared their BSI prior to receipt of the first ceftaroline dose. Each of these populations were analyzed as a whole and further stratified by whether ceftaroline was received as monotherapy or within a combination regimen. For the purposes of this analysis, combination therapy was defined as receipt of ≥ 24 hours of concomitant MRSA-active antibiotic(s). Descriptive statistics, including baseline and clinical characteristics, and outcomes were generated for each population and subgroup. Time to BSI clearance post-ceftaroline initiation was plotted using Kaplan-Meier estimation.

Secondary, exploratory analyses were also conducted in the efficacy population to examine factors associated with clinical failure. The relationship between ceftaroline minimum inhibitory concentration (MIC) and clinical failure was examined by modeling ceftaroline MIC as both continuous and ordinal data via the Mann-Whitney *U* test and Chi-squared test/Fisher's exact test, respectively. Clinical success by ceftaroline dosing frequency was examined via Pearson's chi-squared test/Fisher's exact test while stratifying by the FDA labeled renal dose adjustment categories. Independent predictors of treatment failure were sought through multivariable logistic regression analysis conducted in all patients receiving ceftaroline.

Variables were selected for the regression model based on bivariate comparisons between patients experiencing clinical success or failure through the Pearson's chi-squared test or Fisher's exact test and Student's *t*-test or Mann-Whitney *U* test as appropriate. Variables associated with failure at a *P* value < 0.2 in bivariate analysis with biologic plausibility were entered into the logistic regression model simultaneously and removed in a backward, stepwise fashion, being retained in the model if the adjusted *P* value was < 0.1. Model fit was assessed through the Hosmer-Lemeshow goodness of fit test; models with a non-significant result were considered adequate. Multicollinearity of candidate regression models was assessed via variance inflation factor with values < 3 considered acceptable. All calculations were performed using SPSS Statistics, IBM SPSS software, version 22.0 (IBM Corp., Armonk, NY) with P values < 0.05 considered significant.

RESULTS

In total, 211 patients received ceftaroline for ≥ 72 hours for MRSA BSI during the study period and were included in the safety population. A complete description of patient baseline demographics and clinical characteristics of this population are displayed in supplemental table 1. Ceftaroline was administered every 8 hours in 108 (51.2%) and was given in combination with another MRSA-active antibiotic in 46 (21.8%) of patients. The median (IQR) inpatient duration of ceftaroline was 11 (5 – 15) days. Inpatient adverse reactions were uncommon, with *Clostridium difficile* infection, rash, and neutropenia occurring in 6 (2.8%), 7 (3.3%), and 3 (1.4%) of patients, respectively. Among the three patients experiencing neutropenia, two were

receiving ceftaroline 600mg every 8 hours, while one was receiving 400 mg every 12 hours. The time from ceftaroline initiation to neutropenia onset was 13, 20, and 15 days, respectively.

Patient characteristics and outcomes of the 126 patients included in the efficacy population are located in table 1. The most common MRSA BSI sources were lower respiratory tract (32.5%) and infective endocarditis (24.6%). Ceftaroline was the second (54.0%) or third (35.7%) directed therapy in a majority of cases and the median (IQR) BSI duration pre-ceftaroline was 3 (2.0 – 6.3) days. The most common reasons for ceftaroline use were perceived failure of prior therapy as documented by treating physician (53.2%) and elevated vancomycin MIC (19.8%). Clinical success was observed in 86 (68.3%) of patients in the efficacy population with 28 (22.2%) experiencing in-hospital mortality.

Table 1 also displays the characteristics and outcomes of the monotherapy and combination therapy subgroups within the efficacy population. Patient characteristics in these subgroups were largely similar to the overall cohort. The most common BSI source for the 89 patients receiving monotherapy was lower respiratory tract (35.2%), whereas infective endocarditis (32.6%) was most common among the 37 combination therapy patients. Ceftaroline monotherapy was predominantly used as the second directed therapy (54.0%) with a median (IQR) BSI duration pre-ceftaroline of 3 (2 – 5.5) days. In contrast, ceftaroline combination therapy was the third directed regimen in most cases (69.6%) with a corresponding median (IQR) BSI duration pre-ceftaroline of 4 (2.5 – 9) days. Daptomycin was the most common combination agent, received by 33 (71.7%) of the combination therapy subgroup. Clinical success was observed in 62 (69.7%) and 24 (64.9%) of the monotherapy and combination therapy patients, respectively. Bloodstream infection clearance on ceftaroline

monotherapy occurred in 79 (88.8%) with a median (IQR) BSI duration post-ceftaroline of 2 (1 – 4) days. Among combination therapy patients, clearance on ceftaroline occurred in 36 (97.3%) and the median (IQR) BSI duration post-ceftaroline was 3 (1.5 – 5) days. Time to BSI clearance post-ceftaroline initiation in both monotherapy and combination therapy subgroups is plotted in figure 1.

Bivariate comparisons in the efficacy population between patients experiencing success and failure are shown in supplemental table 2. No difference in ceftaroline MIC was noted between those experiencing success or failure and clinical failure modeled continuously (median [IQR] 0.5 [0.5 – 1] vs. 0.5 [0.5 – 1] mg/L, $P = 0.621$) or ordinally (supplemental figure 1). The proportion of patients experiencing clinical success also did not vary across ceftaroline dosing frequency, overall or when stratified by renal function (supplemental table 3). Based on the bivariate analyses, APACHE II score, comorbid malignancy, lower respiratory tract BSI source, bone/joint BSI source, and ceftaroline dose in mg, were entered into multivariable logistic regression for factors associated with failure. The results of the final multivariable logistic regression model are listed in table 2. APACHE II score and comorbid malignancy were independently associated with failure.

DISCUSSION

Given the widespread burden of MRSA BSI on the healthcare system and the limitations of current standard therapies, this analysis sought to assess ceftaroline as a potential treatment option. The results suggest ceftaroline is effective and safe for MRSA BSI, given as monotherapy or in combination with other MRSA-active antibiotics. Clinical success was observed in nearly 70% of patients and BSI clearance on ceftaroline occurred in more than 90%.

Ceftaroline was the second or third directed therapy in the vast majority of included patients and perceived failure of prior therapy was the documented reason for ceftaroline use in more than half. Thus, these results primarily represent ceftaroline as "salvage" therapy.

These results are consistent with prior observational studies of ceftaroline for MRSA BSI, the majority of which demonstrate success in 70% or more cases with a limited number of adverse effects.(17-21, 23, 24) Due to the robust sample size, the present study is able to build upon previous observational data by evaluating the outcomes of patients receiving ceftaroline monotherapy and combination therapy separately. Although direct comparison with standard MRSA BSI therapies is necessary before drawing firm conclusion on the efficacy of ceftaroline, crude comparisons with previous studies place these results into context. Despite the fact ceftaroline was the second or third directed therapy in most patients in this study, the observed clinical success and mortality rates compare favorably to vancomycin.(6) This echoes the findings of a small comparative analysis of ceftaroline and vancomycin for MRSA BSI.(23) Comparison with prior daptomycin studies is challenging due to the exclusion of BSI secondary to pneumonia from these studies.(9-11) One-third of this cohort was comprised of patients with lower respiratory tract source, which carries a high risk of mortality.(31, 32) Nonetheless, a similar proportion of patients experienced failure compared to a recently published evaluation of daptomycin for MRSA BSI.(11) Collectively these findings suggest ceftaroline has promise for MRSA BSI treatment.

Another notable finding is the time to BSI clearance observed following ceftaroline initiation. Clearance following the initiation of ceftaroline, as monotherapy or in combination, occurred in 50% of patients within 3 days, and in more than 80% of patients within 7 days. This

218 is consistent with previous ceftaroline observational studies and resembles time to MSSA BSI
219 clearance by beta-lactams.(22-24) Clinical data suggest beta-lactams provide quicker BSI
220 clearance relative to vancomycin for Staphylococcal BSI.(8, 33) A potential explanation for this
221 is the ability of beta-lactams, including ceftaroline, to sensitize *Staphylococcus aureus* to killing
222 by human cationic host defense peptides (HDP) of the innate immune system.(24, 34, 35) This
223 interaction is likely mediated by enhanced cationic HDP cell membrane binding through
224 increased membrane negativity and is analogous to the mechanism of the synergy observed
225 between daptomycin and ceftaroline.(35, 36)

226 This analysis also explored factors associated with treatment failure. Not surprisingly,
227 higher APACHE II scores and comorbid malignancy were independently associated with
228 treatment failure. No relationship between ceftaroline MIC or ceftaroline dosing frequency and
229 failure was observed. Although the ceftaroline 600 mg dose was associated with success in
230 bivariate analyses, it was not after multivariable regression. However, these findings should be
231 interpreted with great caution. The ceftaroline MIC distribution was narrow (MIC_{50} 0.5 mg/L;
232 MIC_{90} 1 mg/L) and there was a limited number of isolates at (21) or above (3) the clinical
233 laboratory standards institute susceptibility breakpoint of 1 mg/L.(37) Part of the rationale for
234 more aggressive every 8 hour dosing is to optimize the likelihood of achieving adequate time
235 free drug concentration exceeds the MIC for isolates at the susceptibility breakpoint
236 (1mg/L).(38) Thus it is possible there were too few infections truly necessitating more
237 aggressive dosing in this cohort to detect a difference in outcome across dosing paradigms. It
238 should also be noted that although we attempted to account for patient specific ceftaroline
239 clearance by stratifying by creatinine clearance, this is merely a crude exploratory analysis. This

cannot substitute a careful exposure-response analysis that would require pharmacokinetic sampling and known ceftaroline MIC in all patients. As such, the optimal dosing paradigm for ceftaroline remains undefined, but given the observed tolerability of this regimen, it is reasonable to employ every 8 hour dosing for difficult to treat infections.

There are numerous considerations to bear in mind when interpreting these results. This was a retrospective study and the findings are subject to the caveats associated with this study design. The primary concern is missing data due to incomplete documentation in the medical record. To address this we selected objective and easily measureable outcomes, such as all-cause mortality and BSI duration. Study data were limited to inpatient records, thus efficacy and safety endpoints reflect the short-term. We were unable to assess long-term infection recurrence and adverse reactions, namely neutropenia, may be underrepresented considering this reaction is known to occur with prolonged ceftaroline administration.(39) This analysis included three academic medical centers, and it is unclear if these findings apply to other sites with differing patient populations and practice patterns. Ceftaroline was predominantly given as the second or third directed therapy. Given the impact prior therapy could have on the infection and organism, it is unclear if the observed outcomes, particularly BSI duration post-ceftaroline, would be consistent if ceftaroline was given at MRSA BSI onset. Finally, it is important to note that susceptibility testing was not done centrally but at each individual hospital microbiology laboratory. Minimum inhibitory concentrations were not done via broth microdilution per Clinical Laboratory Standards Institute guidelines, which is used when establishing susceptibility breakpoints.

In conclusion, ceftaroline was well tolerated and demonstrated favorable clinical response rates for MRSA BSI as monotherapy or combination therapy. Bloodstream infection clearance was rapid following ceftaroline initiation in the majority of patients with an active BSI at the start of ceftaroline. This, along with prior observational data, demonstrates the viability of ceftaroline as a potential treatment option for MRSA BSI. This includes BSI secondary to high-inoculum sources, such as infective endocarditis and pneumonia, and following perceived failure of prior therapy. With the limited number of cases where ceftaroline was used as the initial antibiotic therapy, its merit as a first line agent remains unclear. However, these data suggest ceftaroline is ready for direct comparative study with the current standard of care for MRSA BSI.

Funding: The investigators received no funding for execution of this study.

Conflicts of interest: S.L.D is a grant recipient and has served on advisory board of Allergan and Merck & Co. and has served on advisory board of Melinta. M.J.R. is a grant recipient of, consultant for, advisory board member, and is on the speaker's bureau for Allergan, Bayer, Cempra Inc., Merck & Co., The Medicines Company, Sunovian, and Theravance and is supported in part by NIH R21 AI109266-01 and RO1 AI121400-01. All other authors report no potential conflicts.

Acknowledgements: None

282 **REFERENCES**

283 1. **Dantes R, Mu Y, Belflower R, Aragon D, Dumyati G, Harrison LH, Lessa FC, Lynfield R,**
284 **Nadle J, Petit S, Ray SM, Schaffner W, Townes J, Fridkin S.** 2013. National burden of
285 invasive methicillin-resistant Staphylococcus aureus infections, United States, 2011.
286 JAMA internal medicine **173:**1970-1978.

287 2. **Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG, Jr., Hellmich M, Hopkins S, Kern WV,**
288 **Llewelyn MJ, Rieg S, Rodriguez-Bano J, Scarborough M, Seifert H, Soriano A, Tilley R,**
289 **Torok ME, Weiss V, Wilson AP, Thwaites GE.** 2014. Staphylococcus aureus bloodstream
290 infection: a pooled analysis of five prospective, observational studies. J Infect **68:**242-
291 251.

292 3. **Lodise TP, McKinnon PS.** 2005. Clinical and economic impact of methicillin resistance in
293 patients with Staphylococcus aureus bacteremia. Diagnostic microbiology and infectious
294 disease **52:**113-122.

295 4. **Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y.**
296 2003. Comparison of mortality associated with methicillin-resistant and methicillin-
297 susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clinical infectious
298 diseases **36:**53-59.

299 5. **Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW,**
300 **Levine DP, Murray BE, M JR, Talan DA, Chambers HF.** 2011. Clinical practice guidelines
301 by the infectious diseases society of america for the treatment of methicillin-resistant
302 Staphylococcus aureus infections in adults and children. Clin Infect Dis **52:**e18-55.

6. **van Hal SJ, Lodise TP, Paterson DL.** 2012. The clinical significance of vancomycin minimum inhibitory concentration in Staphylococcus aureus infections: a systematic review and meta-analysis. Clin Infect Dis **54:**755-771.

7. **Casapao AM, Leonard SN, Davis SL, Lodise TP, Patel N, Goff DA, Laplante KL, Potoski BA, Rybak MJ.** 2013. Clinical outcomes in patients with heterogeneous vancomycin-intermediate Staphylococcus aureus (hVISA) bloodstream infection. Antimicrob Agents Chemother.

8. **Fowler VG, Jr., Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, Levine DP, Chambers HF, Tally FP, Vigliani GA, Cabell CH, Link AS, DeMeyer I, Filler SG, Zervos M, Cook P, Parsonnet J, Bernstein JM, Price CS, Forrest GN, Fatkenheuer G, Gareca M, Rehm SJ, Brodt HR, Tice A, Cosgrove SE.** 2006. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. The New England journal of medicine **355:**653-665.

9. **Moore CL, Osaki-Kiyan P, Haque NZ, Perri MB, Donabedian S, Zervos MJ.** 2012. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant Staphylococcus aureus with a high vancomycin minimum inhibitory concentration: a case-control study. Clin Infect Dis **54:**51-58.

10. **Murray KP, Zhao JJ, Davis SL, Kullar R, Kaye KS, Lephart P, Rybak MJ.** 2013. Early use of daptomycin versus vancomycin for methicillin-resistant Staphylococcus aureus bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. Clin Infect Dis **56:**1562-1569.

11. **Claeys KC, Zasowski EJ, Casapao AM, Lagnf AM, Nagel JL, Nguyen CT, Hallesy JA, Compton MT, Kaye KS, Levine DP, Davis SL, Rybak MJ.** 2016. Propensity Matched Analysis of Early Daptomycin versus Vancomycin for Methicillin-Resistant S. aureus Bloodstream Infections: Daptomycin Improves Outcomes Regardless of Vancomycin MIC. Antimicrob Agents Chemother.

12. **Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J.** 2005. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. The Journal of infectious diseases **191:**2149-2152.

13. **Barber KE, Ireland CE, Bukavyn N, Rybak MJ.** 2014. Observation of "seesaw effect" with vancomycin, teicoplanin, daptomycin and ceftaroline in 150 unique MRSA strains. Infectious diseases and therapy **3:**35-43.

14. **Sharma M, Riederer K, Chase P, Khatib R.** 2008. High rate of decreasing daptomycin susceptibility during the treatment of persistent Staphylococcus aureus bacteremia. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology **27:**433-437.

15. **Gasch O, Camoez M, Dominguez MA, Padilla B, Pintado V, Almirante B, Martin C, Lopez-Medrano F, de Gopegui ER, Blanco JR, Garcia-Pardo G, Calbo E, Montero M, Granados A, Jover A, Duenas C, Pujol M.** 2014. Emergence of resistance to daptomycin in a cohort of patients with methicillin-resistant Staphylococcus aureus persistent bacteraemia treated with daptomycin. The Journal of antimicrobial chemotherapy **69:**568-571.

16. **Sader HS, Flamm RK, Jones RN.** 2013. Antimicrobial activity of ceftaroline tested against staphylococci with reduced susceptibility to linezolid, daptomycin, or vancomycin from U.S. hospitals, 2008 to 2011. Antimicrob Agents Chemother **57:**3178-3181.

17. **Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, Kaye KS, Mynatt RP, Molloy LM, Pogue JM, Rybak MJ.** 2014. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother **58:**2541-2546.

18. **Ho TT, Cadena J, Childs LM, Gonzalez-Velez M, Lewis JS, 2nd.** 2012. Methicillin-resistant Staphylococcus aureus bacteraemia and endocarditis treated with ceftaroline salvage therapy. The Journal of antimicrobial chemotherapy **67:**1267-1270.

19. **Lin JC, Aung G, Thomas A, Jahng M, Johns S, Fierer J.** 2013. The use of ceftaroline fosamil in methicillin-resistant Staphylococcus aureus endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy **19:**42-49.

20. **Polenakovik HM, Pleiman CM.** 2013. Ceftaroline for meticillin-resistant Staphylococcus aureus bacteraemia: case series and review of the literature. International journal of antimicrobial agents **42:**450-455.

21. **Tattevin P, Boutoille D, Vitrat V, Van Grunderbeeck N, Revest M, Dupont M, Alfandari S, Stahl JP.** 2014. Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study. The Journal of antimicrobial chemotherapy **69:**2010-2013.

22. **Fabre V, Ferrada M, Buckel WR, Avdic E, Cosgrove SE.** 2014. Ceftaroline in Combination With Trimethoprim-Sulfamethoxazole for Salvage Therapy of Methicillin-Resistant Staphylococcus aureus Bacteremia and Endocarditis. Open forum infectious diseases **1:**ofu046.

23. **Paladino JA, Jacobs DM, Shields RK, Taylor J, Bader J, Adelman MH, Wilton GJ, Crane JK, Schentag JJ.** 2014. Use of ceftaroline after glycopeptide failure to eradicate meticillin-resistant Staphylococcus aureus bacteraemia with elevated vancomycin minimum inhibitory concentrations. International journal of antimicrobial agents **44:**557-563.

24. **Sakoulas G, Moise PA, Casapao AM, Nonejuie P, Olson J, Okumura CY, Rybak MJ, Kullar R, Dhand A, Rose WE, Goff DA, Bressler AM, Lee Y, Pogliano J, Johns S, Kaatz GW, Ebright JR, Nizet V.** 2014. Antimicrobial Salvage Therapy for Persistent Staphylococcal Bacteremia Using Daptomycin Plus Ceftaroline. Clinical therapeutics.

25. **Horan TC, Andrus M, Dudeck MA.** 2008. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. American journal of infection control **36:**309-332.

26. **Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG.** 2009. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics **42:**377-381.

27. **Charlson ME, Pompei P, Ales KL, MacKenzie CR.** 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases **40:**373-383.

28. **Knaus WA, Draper EA, Wagner DP, Zimmerman JE.** 1985. APACHE II: a severity of disease classification system. Crit Care Med **13:**818-829.

29. **Stevens V, Lodise TP, Tsuji B, Stringham M, Butterfield J, Dodds Ashley E, Brown K, Forrest A, Brown J.** 2012. The utility of acute physiology and chronic health evaluation II scores for prediction of mortality among intensive care unit (ICU) and non-ICU patients with methicillin-resistant Staphylococcus aureus bacteremia. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America **33:**558-564.

30. National Cancer Institute Cancer Therapy Evaluation Program. Common Toxicity Criteria Manual. Version 2.0. Jun 1999. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf.

31. **Shorr AF, Zilberberg MD, Micek ST, Kollef MH.** 2015. Outcomes associated with bacteremia in the setting of methicillin-resistant Staphylococcus aureus pneumonia: a retrospective cohort study. Crit Care **19:**312.

32. **Soriano A, Martinez JA, Mensa J, Marco F, Almela M, Moreno-Martinez A, Sanchez F, Munoz I, Jimenez de Anta MT, Soriano E.** 2000. Pathogenic significance of methicillin resistance for patients with Staphylococcus aureus bacteremia. Clin Infect Dis **30:**368-373.

33. **Levine DP, Fromm BS, Reddy BR.** 1991. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis. Ann Intern Med **115:**674-680.

34. **Sakoulas G, Okumura CY, Thienphrapa W, Olson J, Nonejuie P, Dam Q, Dhand A, Pogliano J, Yeaman MR, Hensler ME, Bayer AS, Nizet V.** 2014. Nafcillin enhances innate immune-mediated killing of methicillin-resistant Staphylococcus aureus. Journal of molecular medicine (Berlin, Germany) **92:**139-149.

35. **Werth BJ, Sakoulas G, Rose WE, Pogliano J, Tewhey R, Rybak MJ.** 2013. Ceftaroline increases membrane binding and enhances the activity of daptomycin against daptomycin-nonsusceptible vancomycin-intermediate Staphylococcus aureus in a pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother **57:**66-73.

36. **Barber KE, Rybak MJ, Sakoulas G.** 2014. Vancomycin plus ceftaroline shows potent in vitro synergy and was successfully utilized to clear persistent daptomycin-non-susceptible MRSA bacteraemia. Journal of Antimicrobial Chemotherapy**:**dku322.

37. 2014. Clinical and Laboratory Standards Institute. M100-S24: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement., Sixteenth Informational Supplement. CLSI Document M100-S20 ed. CLSI, Wayne, PA.

38. **Canut A, Isla A, Rodriguez-Gascon A.** 2015. Pharmacokinetic/pharmacodynamic analysis to evaluate ceftaroline fosamil dosing regimens for the treatment of community-acquired bacterial pneumonia and complicated skin and skin-structure infections in patients with normal and impaired renal function. International journal of antimicrobial agents **45:**399-405.

430 39. **LaVie KW, Anderson SW, O'Neal HR, Rice TW, Saavedra TC, O'Neal CS.** 2016.
431 Neutropenia Associated with Long-Term Ceftaroline Use. Antimicrob Agents Chemother
432 **60:**264-269.
433

434 **TABLES**

435 **Table 1.** Baseline demographics, clinical characteristics, and outcomes of efficacy population

	Overall N = 126	Monotherapy N = 89	Combination therapy N = 37
Demographics			
Age, years	59 (45.5 – 66.8)	59 (48 – 67)	57 (45 – 66.5)
Male sex	86 (68.3)	50 (56.2)	20 (54.1)
Race			
African American	86 (68.3)	62 (69.7)	24 (64.9)
Caucasian	34 (27.0)	21 (23.6)	13 (35.1)
Hispanic/Latino	1 (0.8)	1 (1.1)	0
Other	5 (4.0)	5 (5.6)	0
Hospital System			
Detroit Medical Center	83 (65.9)	52 (58.4)	31 (83.8)
UF Health – Shands Hospital	30 (23.8)	26 (29.2)	4 (10.8)
Henry Ford Hospital	13 (10.3)	11 (12.4)	2 (5.4)
Comorbidities and past medical history			
Prior antibiotics (90 days)	33 (26.2)	24 (27.0)	9 (24.3)
Prior MRSA infection, (1 year)	20 (15.9)	14 (15.7)	6 (16.2)
Obesity	48 (38.1)	37 (41.6)	11 (29.7)
Diabetes mellitus	47 (37.3)	34 (38.2)	13 (35.1)
Chronic kidney disease	34 (27.0)	25 (28.1)	9 (24.3)
Chronic hemodialysis	26 (20.6)	19 (21.3)	7 (18.9)
Liver disease	20 (15.9)	13 (14.6)	7 (18.9)
Intravenous drug user	24 (19.0)	14 (15.7)	10 (27.0)
Malignancy	7 (5.6)	4 (4.5)	3 (8.1)
HIV/AIDS	8 (6.3)	3 (3.4)	5 (13.5)
Neutropenia[a]	3 (2.4)	2 (2.2)	2 (5.4)
Charlson comorbidity index	3 (2 – 5)	3 (2 – 5)	3 (2 – 5)
Clinical characteristics			
Intensive care unit[b]	45 (35.7)	31 (34.8)	14 (37.8)
APACHE II[b]	16 (12 – 22)	16 (12 – 22)	16 (13 – 22)
Lower respiratory tract source	41 (32.5)	30 (33.7)	11 (29.7)
Infective endocarditis source	21 (24.6)	20 (22.5)	11 (29.7)
Bone/joint source	26 (20.6)	20 (22.5)	6 (16.2)
Intravenous catheter source	20 (15.9)	16 (18.0)	4 (10.8)
Skin/soft tissue source	11 (8.7)	9 (10.1)	2 (5.4)
Other source	22 (17.5)	14 (15.7)	8 (21.6)
Polymicrobial BSI	10 (7.9)	6 (6.7)	4 (10.8)
Vancomycin-susceptible[c]	125 (99.2)	88 (98.9)	37 (100.0)
Daptomycin-susceptible[c,d]	116 (96.7)	80 (96.4)	36 (97.3)
Ceftaroline-susceptible[e]	64 (96.9)	70 (95.9)	24 (100.0)
Treatment information			
Infectious diseases consult	113 (93.4)	79 (91.9)	34 (97.1)
Source control pursued	42 (34.7)	28 (32.9)	14 (38.9)
Vancomycin prior directed therapy	107 (84.9)	74 (83.1)	33 (89.2)
Daptomycin prior directed therapy	48 (38.1)	22 (24.7)	26 (70.3)
Ceftaroline dosing frequency			

Every 8 hours	76 (60.3)	52 (58.4)	14 (37.8)
Every 12 hours	54 (42.9)	33 (37.1)	21 (56.8)
Every 24 hours	6 (4.8)	4 (4.5)	2 (5.4)
Ceftaroline dose			
600 mg	76 (60.3)	55 (61.8)	21 (56.8)
400 mg	19 (15.1)	14 (15.7)	5 (13.5)
300 mg	11 (8.7)	8 (9.0)	3 (8.1)
200 mg	20 (15.9)	12 (13.5)	8 (21.6)
Ceftaroline inpatient duration, days	13 (5 – 21)	13 (5 – 22)	14 (4 – 17)
Combination with daptomycin	28 (22.2)	-	28 (75.7)
Combination with vancomycin	3 (2.4)	-	3 (8.1)
Combination with gentamicin	3 (2.4)	-	3 (8.1)
Combination with rifampin	5 (4.0)	-	5 (13.5)
Outcomes			
Clinical success	86 (68.3)	62 (69.7)	24 (64.9)
In-hospital mortality	28 (22.2)	17 (19.1)	11 (29.7)
Cleared BSI on ceftaroline	115 (91.3)	79 (88.8)	36 (97.3)
BSI duration post-ceftaroline initiation, days	3 (1-4)	2 (1 – 4)	3 (1.5 – 5)
Length of stay post-ceftaroline, days	12 (5.5 – 20)	13 (9 – 20)	15 (8.5 – 22.5)

Data presented as *n* (%) or median (IQR)

Abbreviations: UF, University of Florida; MRSA, methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; APACHE, acute physiology and chronic health evaluation; BSI, bloodstream infection; MIC, minimum inhibitory concentration

[a] Defined as absolute neutrophil count < 500 cells/mm^3 at ceftaroline initiation

[b] At time of index culture

[c] Susceptibility determined by Microscan, Vitek 2, BD Phoenix, or Etest

[d] Daptomycin susceptibility available for 120, 83, and 37 patients in the efficacy population, monotherapy, and combination therapy subgroups, respectively

[e] Ceftaroline susceptibility determined by Etest for 97, 73, and 24 patients in the efficacy population, monotherapy, and combination therapy subgroups, respectively

448 **Table 2.** Multivariable logistic regression analysis for factors independently associated with

449 treatment failure on ceftaroline in efficacy population

450

Variable	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
APACHE II score	1.100 (1.037 – 1.166)	1.093 (1.044 – 1.145)
Malignancy	6.000 (1.111 – 32.405)	3.127 (1.009 – 9.686)
Lower respiratory tract source	2.632 (1.198 – 5.783)	-
Bone/joint source	0.442 (0.153 – 1.274)	-
Ceftaroline dose		
600 mg	-	-
400 mg	3.856 (1.350 – 11.017)	-
300 mg	2.892 (0.785 – 10.651)	-
200 mg	2.314 (0.814 – 6.577)	-

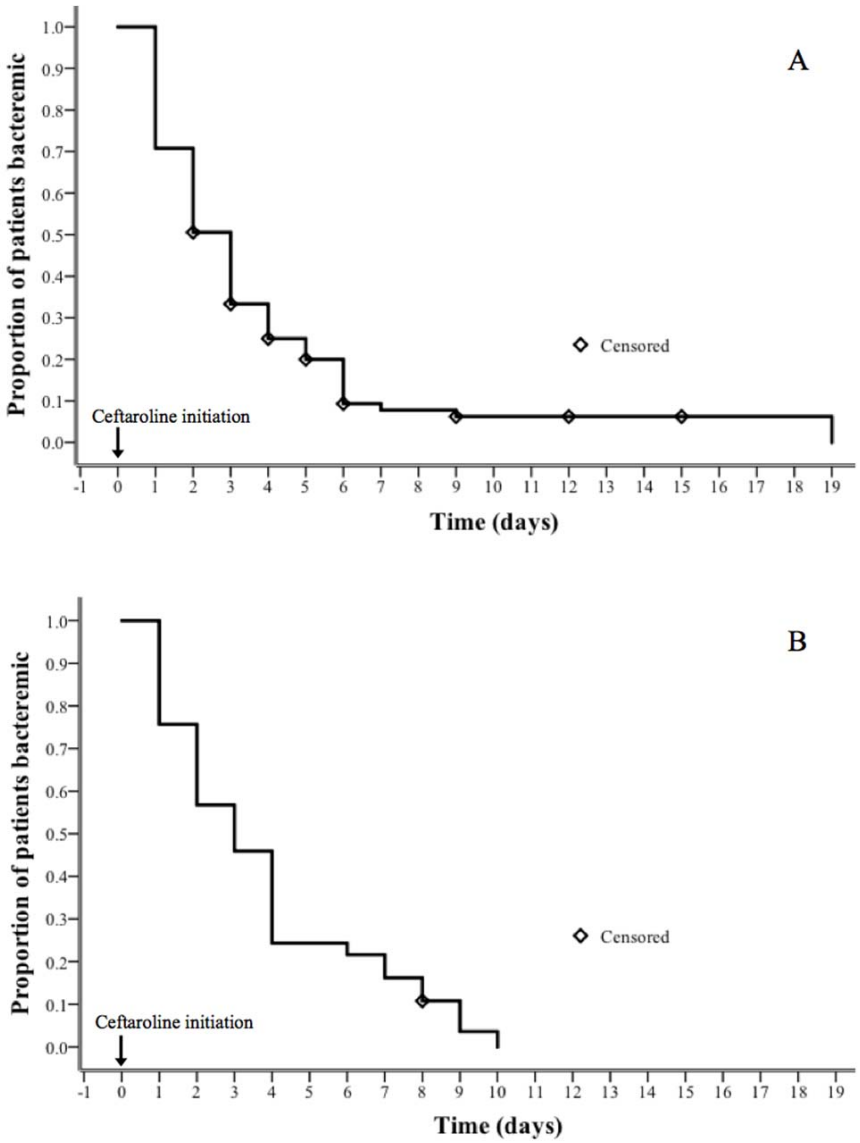
451 Hosmer-Lemeshow goodness of fit test *P* = 0.574; Variance inflation factor < 3 for all variables

452 included at model entry

453 **FIGURES**

454 **Figure 1.** Kaplan-Meier curve of time to bloodstream infection clearance post-ceftaroline

455 initiation in the efficacy population



456