Ceftaroline in Combination With Trimethoprim-Sulfamethoxazole for Salvage Therapy of Methicillin-Resistant *Staphylococcus aureus* Bacteremia and Endocarditis

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No clinical trials have investigated the use of ceftaroline fosamil for salvage therapy of methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis. We report data on 29 patients who received ceftaroline ± another antimicrobial for this indication. Ninety percent of patients had microbiologic cure and 31% had treatment success with a median follow-up of 6 months.

Keywords. bacteremia; ceftaroline fosamil; MRSA; salvage.

Vancomycin and daptomycin are the drugs of choice for the treatment methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis (MRSABIE) [1]; however, therapeutic failures occur in 20%–30% of cases [2–4]. Ceftaroline fosamil is approved by the US Food and Drug Administration for treatment of community-acquired pneumonia and bacterial skin and skin structure infections. Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, has potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) due to high affinity for *S aureus* penicillin-binding proteins 2a [5]. Ceftaroline increasingly has been used off-label in the treatment of MRSABIE, especially in patients failing first-line therapy. Data from case series suggest that ceftaroline is safe and effective for severe MRSA infections with success rates in over 70% of cases; however, these studies were limited by their short-term follow up and inclusion of patients without bacteremia or salvage therapy as the indication for treatment [6, 7]. This study presents clinical outcomes of patients who received ceftaroline for treatment of MRSABIE after they failed to respond to initial therapy.

PATIENTS AND METHODS

We retrospectively analyzed all patients ≥18 years of age admitted to the Johns Hopkins Hospital between August 2011 and August 2013, who received ceftaroline for more than 3 days for therapy of MRSABIE and who did not respond to initial therapy, which was defined as bacteremia lasting ≥7 days or disease progression on therapeutic levels of initial drugs. Cases were identified from pharmacy records, and clinical data were extracted from medical records by the authors. Ceftaroline was dosed at 600 mg every 8 hours intravenously (IV) and was adjusted for patients with glomerular filtration rate (GFR) ≤50 mL/min (400 mg IV q8hs, 300 mg IV q8hs, and 400 mg IV q12hs for GFR 30–50, 15–29, and <15 or hemodialysis, respectively). Trimethoprim-sulfamethoxazole (TMP-SMZ) was dosed at 10–15 mg/kg per day (given in divided doses). Minimum inhibitory concentration (MIC) of vancomycin was determined by the BD Automated System (BD Diagnostics, Sparks, MD). Minimum inhibitory concentration of ceftaroline was determined by disk diffusion or E-test. Methicillin-resistant *Staphylococcus aureus* isolates with intermediate susceptibility to ceftaroline (1.5 μg/mL) by E-test at our laboratory were sent to JMI Laboratories (North Liberty, IA), where MIC was obtained using broth dilution [8]. Duration of bacteremia was the number of days from the first positive blood culture to the last; blood cultures are drawn daily until clearance routinely. Treatment success was defined as absence of microbiologic or clinical recurrence at least 6 weeks after the end of therapy. Microbiologic success was defined as clearance of blood cultures and no recurrence of MRSA at any sterile site after starting ceftaroline therapy. Treatment failure was defined as recurrence of MRSA infection after completion of ceftaroline therapy or death related to MRSA infection. Patients who were lost to follow-up after discharge and who had an appropriate response to therapy at discharge were not considered successes and are reported separately. The Johns Hopkins University School of Medicine Institutional Review Board approved the study with a waiver of informed consent.

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RESULTS

Demographic and clinical characteristics of 29 patients who met eligibility criteria are shown in Table 1. The most common source of infection was endovascular (65%), with 15 cases of infective endocarditis (4 right-sided, 11 left-sided), and 3 cardiac device infections (1 pacemaker and 2 left-ventricular-assisted devices [LVADs]). Nine patients (31%) had soft tissue or bone and joint infection, and 1 patient had pneumonia. Twenty-two patients (76%) had positive blood cultures when ceftaroline was started; the median duration of bacteremia was 9.5 days (interquartile range [IQR], 7, 15) before the switch and 3 days (IQR 2, 5) after the switch. Seven patients were switched to ceftaroline after bacteremia had cleared due to clinical progression on the initial therapy; the median duration of bacteremia in these patients was 13 days (IQR 9, 19), and the median time between bacteremia clearance and initiation of ceftaroline was 1.5 days (IQR 0, 2.5). Six patients (21%) previously treated with vancomycin had MRSA isolates with a vancomycin MIC of 2 μg/mL. Two patients had a ceftaroline MIC of 1.5 μg/mL by E-test; however, they were confirmed to have an MIC of 1 μg/mL by broth microdilution by JMI reference laboratory. Ceftaroline was used alone in 5 patients (17%), in combination with TMP-SMZ in 23 patients (79%), and with daptomycin in 2 patients. Trimethoprim-sulfamethoxazole was avoided in 6 patients due to allergy or underlying renal failure. The most commonly used antibiotic regimen before ceftaroline was vancomycin monotherapy ($n = 16$). Four patients received a non-vancomycin regimen before the switch (daptomycin), whereas the rest ($n = 9$) failed vancomycin in combination with an additional agent or agents (most commonly gentamicin).

Table 1. Demographics, Clinical Data and Outcomes for the Entire Cohort

Age, median (IQR)	54 (47, 62)
Male sex (%)	20 (69)
Race (%)	
White	11 (38)
African American	17 (58)
Comorbidities (%)	
Chronic kidney disease	16 (55)
Chronic kidney disease on hemodialysis	12 (41)
Hypertension	15 (52)
Diabetes mellitus	14 (48)
Coronary artery disease/peripheral vascular disease	8 (28)
Chronic hepatitis C infection	9 (31)
HIV infection	6 (21)
Valvular disease	5 (17)
Sites of infection (%)	
Endovascular	19 (65)
Infective endocarditis*	15 (51)
right-sided	4
left-sided	11
Arterio-venous graft	1 (3)
Cardiac device	3 (10)
Soft tissue, bone and joint	9 (31)
Pneumonia	1 (3)
Duration of MRSAB in days, median (IQR)	
before starting ceftaroline	9.5 (7, 15)
after starting ceftaroline	3 (2, 5)
Concomitant antibiotic use (%)	
Trimethoprim-sulfametoxazole	23 (79)
Daptomycin	2 (6.8)
Outcome (%)	
Microbiologic success	26 (90)
Treatment success	9 (31)
Lost to follow-up	7 (24)
Treatment failure	4 (13)
1 death	
3 recurrent MRSAB	
Deaths unrelated to MRSA infection	9 (31)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSAB, methicillin-resistant *Staphylococcus aureus* bacteremia.

* Concomitant sites of infection: pneumonia $n = 1$, bone and joint $n = 4$, permanent pacemaker $n = 1$, arterio-venous graft $n = 1$.

Twenty-one patients (72%) had an indication for a surgical procedure for source control. Source control was achieved in 62% (13 of 21) of these cases. Central line removal occurred in all patients. Eight patients did not have source control but had clearance of blood cultures on ceftaroline.

Nine patients (31%) were treatment success, with a median follow-up time of 6 months (IQR 4, 10). Four patients (13%) were treatment failure, 3 had recurrent methicillin-resistant *Staphylococcus aureus* bacteremia (MRSAB) 1–6 weeks after completing ceftaroline therapy (1 LVAD infection, 1 undrained spinal abscess, and 1 patient with ongoing intravenous drug use), and 1 patient died from cerebral hemorrhage from septic emboli. Another 7 patients (24%) completed a median duration of ceftaroline therapy of 16 days while hospitalized (IQR 8, 35), with plans for a median duration of 42 days of therapy (IQR 42, 45.5); none had evidence of treatment failure at discharge but were lost to follow-up. In 9 patients (31%), death was not attributed to MRSA infection but due to severe comorbidities and poor functional status. Microbiologic success was observed in 26 patients (90%).

Ceftaroline was discontinued for a drug rash in 1 patient on day 35, for a reversion to vancomycin for easier hemodialysis dosing in 1 patient after 5 days, and for ceftaroline MIC 1.5 μg/mL in 1 patient after 7 days (the isolate was later found to be susceptible).

DISCUSSION

We retrospectively studied 29 patients who received ceftaroline as salvage therapy for MRSAB. Our cohort had severe disease with numerous comorbidities and over half of patients had

infective endocarditis (IE). Like others [9], we observed rapid clearance of blood cultures once the ceftaroline-based regimen was initiated (3 days vs 9.5 days with initial regimen), although it is unknown whether blood cultures would have cleared in the same time frame if the initial therapy had been continued. Treatment failure was observed in 4 patients, 2 of whom had inadequate source control. Our clinical success rate was much lower than other reports (31% vs >70%) [7]. Although others have defined treatment success as no need for further escalation of therapy while on ceftaroline [6] or resolution of signs and symptoms at the end of ceftaroline therapy [7], our patients were considered treatment success if they did not have clinical or microbiologic recurrence at least 6 weeks after completion of therapy. Most patients received TMP-SMZ as a second agent in addition to ceftaroline due to the desire to have a second active agent in the setting of salvage therapy.

There is a recognized need for antibiotics to treat MRSABIE, especially for those patients who fail first-line therapy. The Infectious Diseases Society of America guidelines recommend switching to another agent rather than adding additional agents in cases of persistent bacteremia or decreased susceptibility to vancomycin [1]. In vitro studies demonstrated that ceftaroline has potent activity against staphylococci that show reduced susceptibility to daptomycin and vancomycin [8, 10]. In vivo, ceftaroline was superior to linezolid and vancomycin against MRSA and vancomycin intermediate *Staphylococcus aureus* in an animal model of IE [11]. Polenakovik and Pleiman [7] collected data from 31 patients who received ceftaroline alone or in combination with other anti-MRSA agents for MRSAB after failure of initial therapy. Clinical success was observed in 74% of cases and adverse events in 13% of patients (eosinophilic pneumonia and gastrointestinal intolerance) [7]. Casapao et al [6] evaluated 33 patients with methicillin-resistant *Staphylococcus aureus* infective endocarditis (MRSAIE) treated with ceftaroline; treatment success over a 1-month, follow-up period occurred in 30% of patients.

The limitations of this study are shared by previously reported case series. This is a descriptive retrospective study, and therefore it is not possible to conclude that clinical success was a direct effect of ceftaroline. Several patients were lost to follow-up and could not be called treatment successes; however, in general, patients would likely return to our institution if they had recurrent MRSABIE; thus, we suspect treatment successes were actually higher. Adverse events with ceftaroline could have been underestimated because 24% of patients were lost to follow-up; however, these patients completed ~40% of therapy in the inpatient setting free of adverse events. The majority of patients also received TMP-SMZ; thus, we were unable to fully assess the role of ceftaroline monotherapy in the treatment of refractory MRSABIE.

In summary, our data suggest that ceftaroline with consideration of concomitant TMP-SMZ is a reasonable option for salvage therapy of MRSABIE. Ninety percent of patients had microbiologic success with ceftaroline after prolonged therapy with other agents; however, overall success was limited by the severe underlying illness in this cohort and loss of patients to follow-up.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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