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BRIEF REPORT

Ceftaroline as salvage therapy for complicated MRSA bacteremia: case series and analysis

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Abstract

Introduction Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) is a major cause of morbidity and mortality in hospitalized patients. Ceftaroline fosamil (CPT) is the only available beta-lactam antibiotic with in vitro and in vivo activities against MRSA. There is currently limited clinical experience with CPT in complicated MRSA BSI.

Materials and Methods We report a series of eight patients, including three whose strains had reduced susceptibility to vancomycin.

Results CPT monotherapy was successfully used as salvage therapy for complicated MRSA BSI. The median time to documented clearance was 7 days.

Conclusion Ceftaroline monotherapy is effective for clearance of refractory MRSA BSI related to implanted devices, endocarditis, and orthopedic infections.

Keywords MRSA · VISA · Ceftaroline · Endocarditis · Bacteremia

Background

MRSA bacteremia continues to be a major health problem in hospitalized patients. It is associated with high morbidity and high mortality, increased hospital length of stay, and increased health care costs [1]. Vancomycin and daptomycin are the only antibiotics approved by the US Food and Drug Administration (FDA) for the treatment of MRSA bacteremia and remain the mainstay of treatment [2]. However, therapeutic failures have been increasingly reported with vancomycin [3] and, more recently, with daptomycin [4]. MRSA bloodstream infections secondary to deep-seated foci such as infective endocarditis, medical devices, or abscess are, especially, difficult to treat. The rising rate of vancomycin and daptomycin treatment failure calls for an alternate therapy for complicated MRSA bloodstream infections.

Ceftaroline fosamil is a novel extended-spectrum cephalosporin and is the only clinically available beta-lactam antibiotic with in vitro and in vivo activities against MRSA [5]. It was approved by the FDA in 2010 for the treatment of acute bacterial skin and soft-tissue infections and for community-acquired pneumonia. Ceftaroline has been used off-label as monotherapy to treat MRSA bloodstream infection related to endocarditis [6–8] and in combination with other antibiotics in patients with persistent bacteremia [9, 10].

Objectives

In this case series, we describe patients treated with ceftaroline for complicated MRSA bloodstream infections after the initial treatment failure with vancomycin, daptomycin, linezolid, or a combination of these agents.

Methods

This was a retrospective chart review conducted at Robert Wood Johnson University Hospital (RWJUH, a 600-bed academic medical center in New Brunswick, NJ) which

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is affiliated with Rutgers Robert Wood Johnson Medical School. We identified all adults (> 18 years old) hospitalized between February 22, 2012 and December 1, 2015 with two or more blood cultures positive for MRSA and persistent bacteremia at least 96 h after starting empiric treatment with vancomycin, daptomycin, linezolid, or combinations thereof, who were then treated with ceftaroline. Those who had a minimum of two sets of blood cultures at least 24 h after initiation of ceftaroline salvage therapy were included. Patients who received combination antimicrobial therapy including ceftaroline or who had concurrent infection due to an organism other than MRSA were excluded.

Results

Forty-four orders for ceftaroline fosamil therapy were identified for 37 individual patients, only eight of whom met the inclusion criteria of ceftaroline monotherapy for refractory MRSA bacteremia, after at least 4 days of treatment with either vancomycin, daptomycin, or linezolid. Reasons for exclusion: ten patients did not have positive blood cultures, ten cleared blood cultures prior to initiation of ceftaroline, three received combination therapy with daptomycin, two had sources of bacteremia (pancreatic pseudocyst, pneumonia) not consistent with an intravascular source, two did not receive any doses of ceftaroline, one had concurrent fungemia, and one died within 3 h of initiation of treatment. All eight patients cleared their blood cultures on ceftaroline monotherapy with associated clinical improvement. The mean time to documented clearance was 7 days.

Case reports and clinical outcomes (Table 1)

Case 1

A 71-year-old diabetic woman was admitted with right arm pain and diagnosed with deltoid muscle abscess. Blood cultures were positive for MRSA and work up for persistent MRSA bacteremia with transesophageal echocardiogram (TEE) revealed a 3 × 8 mm mitral valve vegetation associated with an abscess on the atrial surface. She was treated initially with vancomycin, dosed for a trough of 15–20 mg/L (attained by day 3). However, she developed a rash on her extremities, confirmed by biopsy to be leukocytoclastic vasculitis secondary to vancomycin, and was then switched to daptomycin on day 12. She had persistent bacteremia and CT abdomen showed a new splenic infarct consistent with systemic thrombo-embolic phenomenon. The most recent isolate had an MIC of 2 to vancomycin and 1 to ceftaroline, and she was switched to ceftaroline monotherapy 33 days into the hospital course. The last positive blood culture was 5 days later and sustained clearance was documented after 8 days of ceftaroline treatment. The patient's clinical status improved and she was transferred to a rehabilitation facility to complete 6 weeks of ceftaroline.

Case 2

A 61-year-old woman with breast cancer was admitted with fever and weakness after her second cycle of chemotherapy. Blood cultures from both port and peripheral venipuncture grew MRSA with a vancomycin MIC of 1.5. She was initially treated with vancomycin (trough of 15–20 mcg/mL was attained by day 4 of hospitalization) and linezolid 600-mg q12 was added to the regimen on day 3. The port was removed on day 2 of hospital admission. TEE did not show vegetations; however, CT scan revealed a right psoas muscle phlegmon and fluid collection around the right kidney. Given persistent positive blood cultures, on hospital day 9, antibiotics were changed to ceftaroline monotherapy and blood cultures cleared within 2 days. A repeat CT on hospital day 19 showed resolution of the right psoas phlegmon and perinephric fluid. The patient clinically improved and was discharged home on hospital day 21 to complete a 4-week course of antibiotic therapy.

Case 3

A 55-year-old woman on chronic prednisone was admitted with an asthma exacerbation and developed fevers, hypotension, and shoulder pain 3 days into hospitalization. She was found to have MRSA bacteremia and left shoulder septic arthritis. Despite vancomycin treatment, she continued to be febrile. TEE showed a mitral valve vegetation, and mitral valve replacement was performed on hospital day 27. Although the mitral valve culture was negative, her blood cultures continued to be positive prompting a change in antimicrobial therapy from vancomycin to daptomycin. CT scan revealed an abscess in the left adductor muscle with new splenic infarcts. Arthroscopic wash-out of the left shoulder was performed on hospital day 49. The operative specimen did not grow MRSA and blood cultures obtained 1 day after the procedure was sterile. On hospital day 64, while still on daptomycin therapy, the patient developed severe back pain and new fevers. Blood cultures grew vancomycin-intermediate, daptomycin-nonsusceptible Staphylococcus aureus (VISA). MRI of the thoracic spine showed T11–T12 diskitis/osteomyelitis. Daptomycin was stopped and ceftaroline 600-mg q12 h was started. Blood cultures cleared after 6 days of ceftaroline. A repeat MRI showed stable T11–T12 diskitis/osteomyelitis. The patient's symptoms improved without surgical intervention and she was discharged

Table 1 Summary of cases and outcomes

Case	Age (years)/ gender	Source of MRSA bacteremia	Anti-MRSA agents prior to ceftaroline during current hospital admission[a]	Antimicrobial susceptibility results[b]			Ceftaroline dose and duration	Blood cultures results[c]	Microbiologic cure (# days to clearance from initiation of ceftaroline)	Clinical cure
				Vancomycin	Daptomycin	Ceftaroline				
1	71 F	Endocarditis (mitral valve); splenic infarct	Vanco days 2–11; dapto 6 mg/kg daily on days 12–34	2[e]		0.75	600 mg q12 on days 35–51; discharge to complete 6 weeks	**1, 3, 6, 8–10, 13, 20, 21**, 23, 27, **31, 35[d],36,** 37, **40**, 43, 48	Yes (8)	Yes
2	61 F	Port/thigh phlegmon	Vanco days 1–10	1.5		1	600 mg q12 on days 12–21	**1–3, 5, 8, 10, 12[d],**14, 19	Yes (2)	Yes
3	55 F	Endocarditis (mitral valve); L shoulder septic arthritis; splenic infarcts; thoracic spine diskitis/ osteomyelitis	Vanco days 2–10; dapto 6 mg/kg daily on days 7–13; dapto 10 mg/kg daily on days 14–47	2, 4[e], 4[f]	3	0.125	600 mg q12 on days 47–57; discharge to complete 6 weeks	**1, 2, 8, 10, 12, 15,** 18, **21, 23,** 28, **43**, 47[d], **51**, 52, **53**, 55	Yes (6)	Yes
4	68 M	Endocarditis (tricuspid), AICD lead vegetation	Vanco days 1–4; dapto 6 mg/kg daily on days 4–29	2		0.75	200 mg q12 on days 30–60	**1, 2, 4, 7**, 13, **16, 18, 22, 25, 27, 29, 30[d]**, **31, 34, 37,** 42, 50	Yes (12)	Yes
5	74 F	Endocarditis (aortic valve)	Vanco days 2–11; dapto 6 mg/kg daily on days 12–15			1	600 mg q12 on days 15–24; discharge to complete 6 weeks	**1, 3, 8, 11, 13, 15[d],17, 18**, 21, 25	Yes (12)	Yes
6	85 M	AV-graft infection	Vanco days 2–11; dapto 8 mg/ kg q48 on days 12–19				200 mg q12 on days 19–31; discharge to complete 6 weeks	**1, 3, 5, 7, 10, 15, 16[d]**, 23	Yes (4)	Yes

Table 1 continued

Case	Age (years)/ gender	Source of MRSA bacteremia	Anti-MRSA agents prior to ceftaroline during current hospital admission[a]	Antimicrobial susceptibility results[b]			Ceftaroline dose and duration	Blood cultures results[c]	Microbiologic cure (# days to clearance from initiation of ceftaroline)	Clinical cure
				Vancomycin	Daptomycin	Ceftaroline				
7	63 M	Endocarditis (aortic valve); psoas abscess	Dapto 6 mg/kg daily on days 1–9	2[e], 3, 1[g]	4	0.5	600 mg q12 on days 10–23; discharge to complete 6 weeks	**1, 3, 4, 8, 10[d], 12, 13**, 15, **17, 19, 21**, 23, 25	Yes (13)	Yes
8	55 F	Thoracic spine osteomyelitis/ diskitis with epidural abscess from presumed endovascular source	lzd 3–8; dapto 6 mg/kg 8–56; dapto 6 mg/kg 62–65; lzd 66–77	3		26[h]	600 mg q12 on days 77–90; discharge to complete 8 weeks	**1, 2, 3, 4, 6, 7, 8,** 11, **12,** 15, 19, **62, 63, 68, 69, 74, 76[d]**, 79, 85	Yes (3)	Yes

[a]Day 1 is considered the first day of blood cultures positive for MRSA, *vanco* vancomycin, *dapto* daptomycin, *lzd* linezolid

[b]Minimal inhibitory concentration (MIC) performed by E test unless otherwise noted

[c]Day 1 is considered the first day of blood cultures positive for MRSA; numbers in bold indicate dates of positive blood cultures, numbers not bold indicate blood cultures negative for MRSA

[d]Switch to ceftaroline

[e]Microscan WalkAway system (Beckman Coulter, Brea, CA)

[f]Broth microdilution

[g]Repeat E test on same isolate

[h]Kirby–Bauer disc diffusion zone diameter (mm)

to a rehab facility to complete 6 weeks of ceftaroline. She remained stable at 1-year follow-up.

Case 4

A 68-year-old man with insulin-dependent diabetes, history of cardiac arrest, AICD placement, and end-stage renal disease on hemodialysis through a dialysis catheter was admitted with fever, nausea, and vomiting. Vancomycin and ceftriaxone were started empirically. Vancomycin was dosed after dialysis sessions based on serum levels. Blood cultures on admission grew MRSA and repeat blood cultures (one set obtained from peripheral venipuncture and one set from dialysis catheter) were positive on hospital day 2. On day 4 of vancomycin, blood cultures remained positive and daptomycin 6-mg/kg q48 h replaced vancomycin. Despite the initial clearance of bacteremia on hospital day 7, blood cultures again grew MRSA on hospital day 13. A TEE on hospital day 17 showed a 1.6 cm vegetation on the tricuspid valve associated with the ICD lead. ICD leads were removed on hospital day 23, and lead cultures grew MRSA. The patient was considered a poor surgical candidate and no surgical intervention of the valve was planned. Blood cultures remained positive for MRSA, and on hospital day 30, daptomycin was replaced by ceftaroline 200-mg IV every 12 h adjusted for renal function. Blood cultures remained positive for another 7 days and, finally, became sterile after 12 days on ceftaroline. Unfortunately, on hospital day 58, he developed septic shock with polymicrobial bacteremia (*E. coli, E. faecalis*, and *Morganella*) due to an infected decubitus ulcer. He died from multiorgan failure secondary to severe sepsis on hospital day 73.

Case 5

A 74-year-old woman with poorly controlled diabetes mellitus type 2 was admitted with fever and diagnosed with MRSA bacteremia, likely from a sacral decubitus ulcer. She received 3 days of vancomycin prior to discharge to a rehab facility where IV vancomycin was continued. She was re-admitted 4 days later with altered mental status. Blood cultures, which had not cleared by prior hospital discharge, remained positive on readmission. After 12 total days of vancomycin, antibiotics were changed to daptomycin. At this time, transthoracic echocardiogram (TTE) was unremarkable; however, a TEE on day 16 showed a 1×0.3-cm aortic valve vegetation. At this point, blood cultures were still positive and treatment was changed to ceftaroline 600 mg every 12 h. Blood cultures remained positive for 2 more days, but were negative after 6 days of ceftaroline. She was discharged to a rehab facility on day 14 of ceftaroline to complete a 6-week course.

Case 6

A 85-year-old man with CKD stage 4, history of radiation seeds for prostate cancer, chronic suprapubic and left nephrostomy tubes, and history of vancomycin treatment for MRSA bacteremia 6 months prior to admission was admitted with symptoms of weakness and lethargy and diagnosed with acute on chronic kidney failure. He was started hemodialysis through his right AV graft. Five days into hospitalization, he developed a fever and blood cultures grew MRSA (vancomycin MIC = 0.5). Blood cultures remained positive despite 10 days of vancomycin (therapeutic level achieved on day 3), so vancomycin was replaced with daptomycin on hospital day 16. TTE, TEE, and left upper extremity Doppler and tagged white blood cell scan did not reveal a possible source. However, an ultrasound of the left upper extremity showed a 1 cm heterogeneous hypoechoic focus adjacent to the AV graft, presumed to be the source of infection. No surgical intervention was performed. On hospital day 24 daptomycin was stopped and ceftaroline was started. Blood cultures 4 days after the switch were sterile, and the patient was discharged on hospital day 35 to a rehab facility to complete 6 weeks of ceftaroline.

Case 7

A 63-year-old man with diabetes mellitus type 2 was admitted with lethargy and found to have MRSA bacteremia. Approximately 2 months prior to this presentation, he had been hospitalized at a different facility with *Klebsiella* abscesses in the perinephric area, psoas, and thigh requiring multiple CT-guided drainages. His course, there, was complicated by MRSA bacteremia related to a PICC line, for which the PICC line was exchanged and 2 weeks of vancomycin administered. On the current admission, he was treated initially with daptomycin 6 mg/kg daily. TEE performed on the third day of admission showed an aortic valve vegetation that measured greater than 1 cm and he underwent aortic valve replacement on hospital day 6. The valve culture grew MRSA. He remained bacteremic 2-day post-op and antibiotics were changed to ceftaroline on hospital day 10 after MICs for daptomycin and vancomycin were reported as 4 and 2, respectively. Bacteremia persisted and blood cultures on hospital day 17 grew VISA (vancomycin MIC = 3). Repeat testing on the isolate revealed a vancomycin MIC value of 1, suggesting possible heteroresistance. Sterilization of blood cultures was achieved 13 days after initiation of ceftaroline therapy. The patient was discharged on hospital day 30 to a rehab facility to finish 6 weeks of ceftaroline.

Case 8

A 55-year-old woman with severe asthma on 40 mg of chronic prednisone daily, morbid obesity, diabetes mellitus type 2, coronary artery disease, and peripheral vascular disease had multiple recent hospitalizations and antibiotic exposures in the year prior to this presentation. Fevers and persistent back pain 1 month prior to admission prompted MRI evaluation, which revealed T7–T8 diskitis/osteomyelitis with epidural phlegmon; bacterial and acid fast bacterial cultures of bone biopsy were negative and the patient was treated empirically with vancomycin and ceftriaxone, both of which were stopped 7 days into therapy when the patient developed hives. Three weeks later, she was admitted with septic shock and blood cultures grew MRSA and *Enterococcus faecalis*. She was treated with linezolid for 5 days, followed by daptomycin, which achieved sustained sterilization of blood 15 days into her treatment course. TTE, TEE, CT abdomen and pelvis, and tagged WBC were negative. Although no source was identified, the persistently positive blood cultures raised concerns about an endovascular source and she was discharged to a rehab facility to complete 6 weeks of daptomycin. Three days after completing the daptomycin course, she developed fever and complained of worsening back pain prompting readmission, 62 days after her initial admission. Blood cultures grew daptomycin-nonsusceptible VISA (vancomycin MIC = 3). Repeat MRI demonstrated osteomyelitis and epidural abscess extending from T5 to T9 with spinal cord compression. The patient was started on linezolid 600-mg IV q12 h. On the 7th day of that admission (68 days after initial presentation), patient underwent transthoracic corpectomy, laminectomy, and spinal fusion, and operative specimen grew VISA. Despite linezolid treatment and surgical interventions, blood cultures continued to be positive for VISA on hospital day 14. Linezolid was stopped and ceftaroline 600-mg IV q12 h was started on day 16 and within 48 h blood was sterilized. She was discharged 10 days later to finish 8 weeks of ceftaroline and remained stable at 1-year follow-up.

Discussion

Treatment options for serious MRSA infections are limited to only a few active agents. Moreover, *Staphylococcus aureus* infections are difficult to cure, particularly in cases involving an intravascular source. Ceftaroline, the only available beta-lactam with activity against MRSA, is a much needed addition to the antibiotic armamentarium. An evaluation of 1 strain of MRSA that was grown in low-concentration ceftaroline containing media demonstrated enhanced activity by neutrophils compared to the same strain grown in media that did not have antibiotics [9]. This in vitro experiment demonstrated that ceftaroline enhanced innate bactericidal activity against MRSA suggesting ceftaroline alone, rather than in combination with another antibiotic, can be sufficient for treatment of serious MRSA infections.

Other case series have described successful use of ceftaroline for the treatment of complex MRSA infection. Lin and colleagues described ten cases of deep-seated MRSA infections, including five cases of endocarditis, one prosthetic joint, and one osteomyelitis [7]. All isolates were vancomycin susceptible. Four of these seven cases had clinical cure with ceftaroline treatment using various dosing strategies. Ho et al. described six cases of MRSA bacteremia in which three patients had endocarditis (one patient's strain was VISA) and one patient had septic thrombophlebitis [6]. All of the patients had resolution of bacteremia using ceftaroline 600 mg dosed every 8 h for 2–6 weeks, some of whom were then switched to linezolid or vancomycin to complete therapy. Of the 31 cases described in another case series, one patient who had endocarditis due to VISA was treated with 1200-mg total daily dose of ceftaroline resulting in a clinical cure [8]. Another group described cure of two VISA infections using a combination of ceftaroline and daptomycin [9].

This study adds to the body of literature supporting the efficacy of ceftaroline alone for the treatment of severe intravascular infection. In addition, the successful outcomes of our three patients with VISA support the effectiveness of ceftaroline against *Staphylococcus aureus* with reduced susceptibility to vancomycin. As with prior published reports, our study is a case series with inherent biases. The clearance of bacteremia was often not immediate and it is unclear if the eventual cure can be directly attributed to ceftaroline. Similar limitations will persist until randomized clinical trial data become available.

Conclusions

In this case series, we describe the efficacy of ceftaroline monotherapy for clearance of refractory MRSA BSI related to implanted devices, endocarditis, or orthopedic infections—all conditions typically characterized by high rates of treatment failure, including three patients with strains of MRSA not fully susceptible to vancomycin. Randomized studies are still needed to compare the efficacy of ceftaroline monotherapy versus combination therapy of ceftaroline with the other agents to determine the optimal treatment of complicated MRSA BSI.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Liu C, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis. 2011;52:285–92.
2. Naber CK. *Staphylococcus aureus* bacteremia: epidemiology, pathophysiology, and management strategies. Clin Infect Dis. 2009;48:231–7.
3. Charles PG, et al. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clin Infect Dis. 2004;38:448–51.
4. Bayer AS, Schneider T, Sahl HG. Mechanisms of daptomycin resistance in *Staphylococcus aureus*: role of the cell membrane and cell wall. Ann N Y Acad Sci. 2013;1277:139–58.
5. Jorgenson MR, DePestel DD, Carver PL. Ceftaroline fosamil: a novel broad-spectrum cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*. Ann Pharmacother. 2011;45:1384–98.
6. Ho TT, et al. Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. J Antimicrob Chemother. 2012;67:1267–70.
7. Lin JC, et al. The use of ceftaroline fosamil in methicillin-resistant *Staphylococcus aureus* endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. J Infect Chemother. 2013;19:42–9.
8. Polenakovik HM, Pleiman CM. Ceftaroline for meticillin-resistant *Staphylococcus aureus* bacteraemia: case series and review of the literature. Int J Antimicrob Agents. 2013;42:450–5.
9. Sakoulas G, et al. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. Clin Ther. 2014;36:1317–33.
10. Fabre V, et al. Ceftaroline in combination with trimethoprim-sulfamethoxazole for salvage therapy of methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis. Open Forum Infect Dis. 2014;1:046.