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REVIEW ARTICLE

Ceftaroline for Severe Methicillin-Resistant *Staphylococcus aureus* Infections: A Systematic Review

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Ceftaroline is approved by the Food and Drug Administration for acute bacterial skin and skin-structure infections and community-acquired bacterial pneumonia, including cases with concurrent bacteremia. Use for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections has risen for a multitude of reasons. The aim of this article is to review the literature evaluating clinical outcomes and safety of ceftaroline prescribed for serious MRSA infections. We conducted a literature search in Ovid (Medline) and PubMed for reputable case reports, clinical trials, and reviews focusing on the use of ceftaroline for treatment of MRSA infections. Twenty-two manuscripts published between 2010 and 2016 met inclusion criteria. Mean clinical cure was 74% across 379 patients treated with ceftaroline for severe MRSA infections. Toxicities were infrequent. Ceftaroline treatment resulted in clinical and microbiologic cure for severe MRSA infections. Close monitoring of hematological parameters is necessary with prolonged courses of ceftaroline.

Keywords. ceftaroline; methicillin-resistant *Staphylococcus aureus* (MRSA); bacteremia; endocarditis; pneumonia.

Ceftaroline is an intravenous, bactericidal cephalosporin approved by the US Food and Drug Administration (FDA) in 2010 for the treatment of acute skin and skin-structure infections (ABSSSI) caused by susceptible microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also approved for community-acquired bacterial pneumonia (CABP), including cases with concurrent bacteremia caused by susceptible microorganisms excluding MRSA [1]. Use for concomitant bacteremia in CABP was approved by the FDA in 2015. Ceftaroline is formulated as a zwitterion, rendering it poorly water soluble and therefore synthesized as a prodrug, ceftaroline fosamil for safe administration [2]. The molecular structure confers an increased binding affinity to penicillin-binding protein 2a (PBP-2a), which augments its activity against MRSA. This quality is unique to ceftaroline as compared with all other currently approved cephalosporins, which has resulted in increased interest for its use in the treatment of refractory MRSA infections.

Vancomycin remains first-line therapy for severe MRSA infections; however, clinical failures, poor tolerance, and elevated minimum inhibitory concentrations (MICs) with vancomycin are a concern, especially in severe infections with prolonged treatment courses. Nephrotoxicity with vancomycin remains troublesome and may occur in up to 43% of patients, especially when used concomitantly with other nephrotoxic agents [3]. As a result, the use of daptomycin, linezolid, telavancin, tedizolid, oritavancin, and dalbavancin for the treatment of MRSA infections has been increasing [4]. Ceftaroline has demonstrated clinical success as an alternative to these agents and is endorsed by the Infectious Diseases Society of America for certain MRSA infections, including severe MRSA ABSSSIs [5]. Recommended dosing of ceftaroline is 600 mg every 12 hours; however, in severe infections clinicians may dose ceftaroline every 8 hours. This regimen is often used because pharmacokinetic studies have suggested optimal time-dependent killing with more frequent dosing, but superiority has yet to be proven clinically [6].

Clinical Assessment Program and Teflaro(R) Utilization Registry (CAPTURE) conducted a phase IV, observational registry study of ceftaroline use for MRSA CABP, either alone or in combination with other antibiotics—resulted in 66% clinical success (n = 42/64 patients) [7]. Additionally, two phase III studies, ceftaroline versus vancomycin in skin and skin structure infections (CANVAS-1 and CANVAS-2), showed similar cure rates of ceftaroline compared with vancomycin plus aztreonam combination therapy against MRSA ABSSSIs: 93.4% (n = 142/152) and 94.3% (n = 115/122), respectively [8]. These results have supported a role of ceftaroline in the treatment of MRSA CABP and ABSSSIs.

Staphylococcus aureus is the most frequent causative organism of bacteremia in North America and infective endocarditis

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Table 1. Clinical Outcomes Report

Authors	Treatment	Patient Population	Patient No.	Study Design	Clinical Success Rate	Median Time to Culture Clearance	Ceftaroline related-ADE Rate	Notes
Multiple Infections								
Ho, Cadena, Childs. 2012. [10]	CPT 600mg q8-12h	MRSA bacteremia and IE	6	Case series	83.3%	2 days	None reported	1 bacteremia patient died due to comorbidities
Lin et al. 2012. [11]	CPT 600mg q8-12h	MRSA IE, pneumonia, bone and joint infections	10	Case series	60%	3 days	60%	2 patients died from comorbidities; 1 died due to poor source control; ADE: rash, CDI, eosinophilia
Polenakovik, Pleiman. 2013. [12]	CPT 600mg q8-12h[a]	MRSA bacteremia and IE	31	Retrospective review	74.2%	3.5 days	12.9%	2 patients died due to comorbidities; ADE: eosinophilia, rash, CDI
Fabre, Ferrada, Buckel. 2014. [13]	CPT 600mg q8h ± TMP-SMX 10-15mg/kg/day[d]	MRSA bacteremia and IE	29	Retrospective review	31%	3 days	3.4%	7 patients were lost to follow-up; 1 patient died from septic emboli; ADE: rash
Casapao et al. 2014. [14]	CPT 600mg q8-12h	MRSA bacteremia subgroup	241	Retrospective review	78.3%	Not reported	None reported	Higher rates of ADEs in patients treated off-label
CNS Infections								
Kuriakose, Rabbat, Gallagher. 2015. [15]	CPT 600mg q8h	VP-shunt related MRSA meningitis	1	Case report	100%	Cleared upon shunt removal	None reported	—
Balouch, Bajwa, Hassoun. 2015. [16]	CPT 600mg q8h + RIF 300mg BID	MRSA meningitis	1	Case report	100%	1 day	None reported	Culture clearance based on blood cultures; CSF cultures not repeated
Bucheit, Collins, Joshi. 2014. [17]	CPT 600mg q12h	MRSA epidural abscess	1	Case report	100%	1 day	None reported	Clearance based on blood; abscess cultures not repeated
Nosocomial Pneumonia								
Kaye, Udeani, Cole. 2015. [18]	CPT ± concomitant antibiotics	MRSA nosocomial pneumonia	12 HAP 7 VAP	Retrospective review	58.3% 57.1%	Not reported	3%	Death rates not reported specifically for MRSA; ADE: unspecified
Pasquale, Tan, Trienski. 2015. [19]	CPT 600mg q12h	MRSA nosocomial pneumonia	10	Case series	60%	Not reported	None reported	3 patients died due to comorbidities; 1 patient relapsed after 1 week off antibiotics
Combination Therapy								
Rose, Schulz, Andes. 2012. [23]	CPT 200mg q12h + DAP 6mg/kg q48h	*S. aureus* IE	1	Case report	100%	4 days	None reported	Patient died after culture clearance due to comorbidities
Baxi, Chan, Jain. 2015. [24]	CPT 400mg q12h + DAP[b]	*S. aureus* IE	1	Case report	100%	11 days	None reported	—
Sakoulas et al. 2014. [25]	CPT 200mg q12h-600mg q8h + DAP[b]	Staphylococcal bacteremia	26	Case series	96%	2 days	None reported	1 patient died due to comorbidities
Cunha, Gran. 2015. [26]	CPT 600mg q12h + DAP 12mg/kg q24h	MRSA prosthetic-valve IE	1	Case report	100%	4 days	None reported	—
Sundragiri, Vallabhajosyula, Haddad. 2015. [27]	CPT + DAP[c]	MRSA IE	1	Case report	0%	No clearance	None reported	Patient remained septic and died eventually died

Abbreviations: CPT, ceftaroline; RIF, rifampicin; DAP, daptomycin.
[a]Concomitant antimicrobials given including linezolid, DAP, gentamicin, RIF and tigecycline.
[b]Variety of DAP doses were used.
[c]Doses unspecified.
[d]Twenty-three patients also received SMX-TMP and 2 received DAP.

(IE) internationally with 26% and 31.4% prevalence, respectively [9]. There is increasing evidence of the utility of ceftaroline in the treatment of severe MRSA infections, such as bacteremia and IE [10–14]. Case reports and small retrospective studies have also supported success with ceftaroline in the treatment of nosocomial pneumonia, orthopedic infections,

and central nervous system (CNS) infections caused by MRSA [15–19]. Here we have compiled the existing published reports into a concise review of the clinical outcomes and adverse events associated with ceftaroline for the treatment of serious MRSA infections.

METHODOLOGY

The English-language literature in PubMed, Ovid (Medline) and Cochrane Databases of Systemic Reviews, Health Technology Assessment, and National Health Service Economic Evaluation Database was searched using the search term "ceftaroline" from 2010 to 2016. A total of 243 articles were identified. Articles were considered for inclusion if they were case reports, studies, or reviews focusing on the non-FDA-approved use of ceftaroline for severe MRSA infections. After careful review of each article, 22 articles were included in the final analysis.

RESULTS

Clinical Outcomes

Currently available literature on the use of ceftaroline for severe MRSA infections grouped by disease state is summarized herein (Table 1).

Bacteremia, Infective Endocarditis, and Other Severe Infections

Ho et al published a series of 6 patients treated with ceftaroline for MRSA bacteremia or IE [10]. All cases were refractory to vancomycin or daptomycin therapy. All MRSA isolates had a ceftaroline MIC ≤ 0.5 mg/L and a vancomycin MIC ≥ 1.5 mg/L. All patients with IE received ceftaroline 600 mg intravenously every 8 hours. Of the 4 patients with IE, 1 received a full 6-week course of ceftaroline, 2 were treated for 3 weeks with ceftaroline then transitioned to oral linezolid for 3 weeks, and 1 received ceftaroline for 2 weeks followed by vancomycin for 4 weeks. One patient without evidence of IE received 3 weeks of ceftaroline 600 mg intravenously every 8 hours followed by daptomycin. The sixth patient was treated with ceftaroline 600 mg intravenously every 12 hours for bacteremia but died due to pulmonary failure unassociated with infection. Five patients achieved complete sterilization of cultures on ceftaroline after a median of 2 days. Overall 83.3% of patients were deemed clinically cured. Duration of follow-up is not noted in the case series, and no adverse drug events were reported.

In another case series, 10 patients were treated with ceftaroline 600 mg every 8 or 12 hours for MRSA infections [11]. Five had IE, 2 had pneumonia, and 4 had orthopedic infections; there were multiple diagnoses in 2 patients. All cases were refractory to vancomycin or daptomycin therapy. Seven patients achieved complete sterilization of blood cultures on ceftaroline, and 6 of the 10 patients were deemed to have complete clinical cure. Three patients died, 1 due to an infected cardiac device and the other 2 from comorbidities; 1 evidenced microbiological cure before death. The final patient did not have resolution of prosthetic joint infection on ceftaroline. Therapy was changed to vancomycin and rifampin, and eventually surgical removal of the infected joint was required for cure. No association between clinical cure and dosing interval was noted. Two patients developed rash, 3 developed *Clostridium difficile* infections (CDIs), and 3 developed eosinophilia at 3–41 days from initiation of therapy.

Polenakovik et al conducted a retrospective review of 31 patients who received ceftaroline 600 mg intravenously every 8 or 12 hours with or without concomitant antimicrobials for MRSA bacteremia [12]. All cases were refractory to standard therapy, including vancomycin. Methicillin-resistant *S. aureus* isolates had a ceftaroline MIC of 0.38–1 mg/L and a vancomycin MIC ≥ 1 mg/L. Sources of bacteremia were varied: 7 from central-venous catheter (CVC), 6 with ABSSSIs, 5 with intravenous drug use, 3 with pneumonia, 1 with an orthopedic implant and vascular graft, 9 with IE, and 8 with unknown source. Several patients had multiple sources identified. Blood cultures were cleared after a median of 3.5 days. After a median duration of 30 days of treatment with ceftaroline, 74.2% (n = 23 patients) were deemed to have achieved a clinical cure. The dosing interval was not associated with improved clinical success. Two patients died from comorbidities, and all cases of relapse were due to retained prosthetic materials. Adverse drug effects

Table 2. Safety Reports

Reference	Treatment	Patient No.	Study Design	ADE	ADE Rate	Median Time to ADE	
Varada, Sakoulas, Lei. 2015. [29]	CPT 600mg q8-12h + CLI	55	Retrospective review	Neutropenia	7.3%	22 days	ANC 0cells/mm^3 for all patients
LaVie et al. 2015. [30]	CPT 600mg q8-12h	39	Retrospective review	Neutropenia	18%	24 days	10% of patients developed ANC < 500 cells/mm^3
Jain et al. 2014. [31]	CPT 600mg q8-12h	12	Retrospective review	Neutropenia Anemia Severe rash	33.3% 33.3% 16.6%	22 days	—
Furtek et al. 2016. [32]	CPT	67	Retrospective review	Neutropenia	14% 21%	≥14 days ≥21 days	ANC ranged from 0-1605cells/mm^3

Abbreviations: ANC, absolute neutrophil count; CLI, clindamycin; CPT, ceftaroline

[a]Patients in all four studies had received a variety of concomitant antimicrobials throughout therapy.

with ceftaroline were minimal but included 3 cases of peripheral eosinophilia, 1 rash, and 2 CDIs. The results of this study should be interpreted with caution because it excluded patients receiving less than a week of ceftaroline and included patients receiving combination antimicrobial therapy, which may confound results.

Another retrospective review included 29 patients who were treated with ceftaroline 600 mg intravenously every 8 hours primarily with concomitant trimethoprim/sulfamethoxazole or daptomycin for MRSA IE [13]. Patients with MRSA IE who failed to respond to initial therapy and who received ceftaroline for >3 days were included in the review. All MRSA isolates were tested for ceftaroline susceptibility, and all had a ceftaroline MIC < 1 mg/L. Vancomycin was used prior to ceftaroline in 16 patients, of whom 6 had MRSA isolates with a vancomyin MIC of 2 mg/L. Sources of bacteremia included: 15 with IE, 3 with cardiac devices, 9 with ABSSSIs or osteomyelitis/septic arthritis, 1 with pneumonia, and 1 with unknown source. After a median of 3 days (interquartile range IQR] = 2–5 days) of therapy, 26 patients (90%) achieved sterilization of blood cultures on ceftaroline. Nine (31%) had complete clinical cure at 6 months, and 24% of patients were lost to follow-up. Four (13%) failed therapy, 3 due to relapse with recurrent intravenous drug use or poor source control. One died of MRSA septic emboli. Nine patients (31%) failed treatment and died from unrelated concomitant conditions. Only 1 patient discontinued ceftaroline therapy due to rash on day 35 of treatment. Because of the high rate of combination therapy, results should be interpreted with caution.

A retrospective review of the use of ceftaroline for 527 patients with a variety of infections included a large number of patients with MRSA infections [14]. Patients were included if they received ceftaroline for >72 hours. One hundred forty-eight patients had blood stream infections, of which *S. aureus* was the isolated pathogen in 89.9% (n = 133/148) of cases. Among those patients with positive blood cultures for *S. aureus*, 92.4% (n = 123) were positive for MRSA. All patients received ceftaroline for a median duration of 9 days (IQR = 4–16 days). Among the patients who had *S. aureus* bacteremia, 90.2% (n = 120/133) had follow-up microbiology data available, and of these, 90.8% (n = 109/120) achieved sterilization of blood cultures. However, it should be noted that patients with concomitant *S. aureus* IE or pneumonia had high rates of clinical failure: 30.3% and 27.6%, respectively.

Central Nervous System Infections

There are only 3 published cases of use of ceftaroline for treatment of MRSA infections of the CNS.

A single case report documents use of ceftaroline for treatment of MRSA infection in the cerebrospinal fluid with underlying ventriculoperitoneal shunt [15]. The ventriculoperitoneal shunt was removed, and the patient was treated with ceftaroline 600 mg every 8 hours (MIC of 1 mg/L). After 24 days, the patient had clinically improved and was prescribed oral linezolid for 1 additional week. Central nervous system penetration, which was evaluated after meningeal inflammation had subsided, was 4.1% and 3.5% at 1.5 hours after infusion and 0.5 hours before the next dose, respectively. These findings are comparable with other beta-lactams.

Balouch et al reported a single case of MRSA bacteremia and meningitis treated with ceftaroline 600 mg every 8 hours and rifampicin 300 mg twice daily [16]. The MRSA isolate had elevated MICs to vancomycin (MIC of 2 mg/L) and daptomycin (MIC of 1 mg/L), but the MIC to ceftaroline was 0.25 mg/L. Blood cultures sterilized after 1 day of ceftaroline and rifampicin therapy. Clinical cure was achieved after 8 weeks of ceftaroline therapy with rifampicin for the first 2 weeks. There was no recurrence of infection at 1-year follow-up. No ceftaroline-associated adverse events were reported.

An additional single case report describes the use of ceftaroline to treat MRSA bacteremia and an epidural abscess [17]. The patient was initially treated with 4 days of vancomycin, 7 days of daptomycin, and surgical debridement but continued to do poorly. The MRSA isolate had a vancomycin MIC of 1.5 mg/L, a daptomycin MIC of 0.38 mg/L, and a ceftaroline MIC of 0.5 mg/L. Cultures became negative 1 day after initiation of ceftaroline. The patient was treated with a 4-week course of ceftaroline 600 mg every 12 hours and achieved clinical cure without a reported adverse event.

Nosocomial Pneumonia

A retrospective review of 19 patients in the CAPTURE study examined clinical outcomes with the use of ceftaroline for MRSA hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) [18]. Twelve patients had MRSA HAP, and 7 patients had MRSA VAP. Prior antibiotic failure was the reason for ceftaroline initiation in the majority of cases. After a mean duration of ceftaroline therapy of 6.9 days for HAP and 7.7 days for VAP, clinical cure occurred in 58.3% and 57.1% of patients, respectively. Only 1 unspecified adverse drug reaction was reported.

Pasquale et al reported 10 cases of MRSA nosocomial pneumonia treated with ceftaroline 600 mg intravenously every 12 hours [19]. Therapy ranged 4–28 days with ceftaroline and was preceded by alternative antibiotics, including vancomycin, in 9 patients. Seven patient isolates were notable for a vancomycin MIC ≥ 1.5 mg/L. Six patients achieved a clinical cure. One patient relapsed a week after completion of therapy, and 3 transitioned to palliative care before treatment completion.

Combination Therapy With Daptomycin

Since the first publication describing daptomycin and antistaphylococcal beta-lactam synergism in 2004, many case reports using ceftaroline with daptomycin have emerged [20–23].

Rose et al described a case of MRSA IE treated with renally dosed ceftaroline 200 mg every 12 hours in combination with daptomycin 6 mg/kg every 48 hours [23]. The patient had clinical worsening after 11 days on daptomycin monotherapy before the addition of ceftaroline. The MRSA isolate had a ceftaroline MIC of 1 mg/L and a daptomycin MIC of 1 mg/L. After ceftaroline was initiated, blood cultures cleared in 4 days, and the MRSA daptomycin MIC, when used in combination with ceftaroline, was reduced to 0.06 mg/L. No adverse events were reported throughout the course of therapy. The patient was discharged to hospice because of comorbid conditions.

Another case report documented the success of combination therapy for MRSA IE despite a high daptomycin MIC [24]. The patient had persistent MRSA bacteremia for 11 days on vancomycin, and later isolates had a vancomycin MIC of 4 mg/L. The MRSA isolate also had a high daptomycin MIC at 4 mg/L, but ceftaroline's MIC was low at 0.5 mg/L. Combination therapy with renally dosed ceftaroline 400 mg every 12 hours and daptomycin 10 mg/kg after days 1 and 2 each week of hemodialysis and 12 mg/kg after day 3 was initiated [24]. After an additional 11 days, blood cultures cleared without recurrence or adverse events.

A case series of 26 patients throughout the United States who were treated with ceftaroline in combination with daptomycin 6–10 mg/kg/d for persistent staphylococcal bacteremia included 22 MRSA cases (2 of which had vancomycin MICs of 3–4 mg/L), 2 methicillin-susceptible *S. aureus* (MSSA) cases, and 2 methicillin-resistant *S. epidermidis* cases [25]. Doses of ceftaroline ranged from 200 mg every 12 hours to 600 mg every 8 hours. After a median of 2 days, blood cultures cleared with combination therapy in 25 patients (96%). One patient died from comorbid conditions. No adverse events related to ceftaroline use were reported.

One case reported success of combination salvage therapy with ceftaroline and daptomycin for MRSA prosthetic valve IE after failure of multiple other agents [26]. The patient had persistent bacteremia despite courses of vancomycin, quinupristin/dalfopristin, and linezolid. The MRSA isolate had a vancomycin MIC of 2 mg/L, quinupristin/dalfopristin MIC of 0.5 mg/L, and a linezolid MIC of 2 mg/L. Therapy was subsequently changed to daptomycin 12 mg/kg/d plus ceftaroline 600 mg every 12 hours. After 4 days, the patient's blood cultures became negative and remained negative after a total of 6 weeks of therapy without adverse events.

Finally, 1 patient had recently been treated with daptomycin for MSSA IE, achieved negative blood cultures, and received a total of 6 weeks of therapy [27]. Daptomycin was prescribed due to its ease of use as the patient was an intravenous drug user. The patient clinically worsened, and blood cultures became positive again within 2 weeks after discontinuation of therapy. *Methicillin-resistant S. aureus* was isolated, which had a newly increased vancomycin MIC of 2 mg/L. Combination therapy with ceftaroline and daptomycin was initiated, and the patient underwent cardiac surgery for removal of the infected valve. However, the patient remained septic, required vasopressors, and developed acute kidney injury. Blood cultures continued to be positive, and care was transitioned to comfort only, and the patient died.

DISCUSSION

Ceftaroline is FDA approved for the treatment of ABSSSI and CABP [1]. The FDA also recently updated the label to include CABP with concomitant bacteremia. Clinical failures with vancomycin and the emergence of MRSA isolates with rising MICs to vancomycin have led to the increased use of ceftaroline in more severe MRSA infections. This review aims at evaluating ceftaroline for treatment of severe MRSA infections.

In this review we found ceftaroline to be well tolerated and a potentially effective agent for the treatment of severe and refractory MRSA infections of several different organ systems. However, because our review contains primarily selected case series that frequently involved other modalities of treatment or combination therapy, no conclusions can be reached about the efficacy of ceftaroline compared with other agents. Despite advances in management, MRSA bacteremia and IE still confer significant morbidity and mortality [9]. Most studies evaluating patients with MRSA bacteremia included patients with IE [10–14]. Clinical success rates were difficult to determine for 1 specific infection. Overall, ceftaroline salvage therapy in patients with MRSA bacteremia with or without IE demonstrated an overall success rate of approximately 80%. With vancomycin clinical failure rates reported up to 24% in MRSA bacteremia, ceftaroline is an attractive alternative [29]. Bone and joint infections are another major cause of morbidity and mortality. Minimal data are available for this indication, but case reports suggest a potential role for ceftaroline in the treatment of orthopedic infections [11–14].

FDA approval of ceftaroline is specific to CABP not caused by MRSA as well as any concurrent bacteremia [1]. Recent studies describe clinical experience using ceftaroline in nosocomial pneumonia, including those caused by MRSA [18, 19]. These publications suggest that ceftaroline may be an effective alternative therapy for MRSA HAP and VAP in specific cases.

Additionally, novel use of the combination of daptomycin with an antistaphylococcal beta-lactam for intractable MRSA infections was first published in 2004 [20–23]. Multiple published case reports have since documented clinical success of this combination therapy using ceftaroline for MRSA bacteremia and IE [23–27]. Other beta-lactams may provide similar synergistic effects; therefore ceftaroline may not be unique in this regard. Future data are necessary to further evaluate combination regimens.

In the studies reviewed here, the dose of ceftaroline varied from 600 mg every 8 hours to every 12 hours. Because

beta-lactams exhibit time-dependent bactericidal activity, it is possible that more frequent dosing may increase ceftaroline's pharmacodynamic effects when treating severe refractory MRSA infections; however, this would need to be confirmed by a clinical trial. Adverse events associated with the higher dose (600 mg every 8 hours) administered in the articles summarized here were infrequently reported.

Overall reports of adverse drug events with short courses of ceftaroline were minimal in studies included in this review: rash (1.1%), CDI (1.3%), and eosinophilia (1.6%). These findings were similar to previously reported incidences from clinical trials when ceftaroline was used for <7 days of treatment. Additionally, agranulocytosis is listed as a postmarket adverse event on the FDA Medwatch [28]. Several recent safety studies have evaluated this and reported agranulocytosis complicating 13% of courses of ceftaroline treatment, which are summarized in Table 2 [29–32]. A few cases were severe with an absolute neutrophil count of 0 cells/mm [29]. In these studies, patients were treated with ceftaroline for longer courses of treatment (>7 days), and these have been associated with an increased risk for neutropenia [33]. Patients receiving ceftaroline for prolonged courses (≥21 days) should be closely monitored for leukopenia.

Only 4 of 8037 MRSA isolates in Europe have demonstrated ceftaroline resistance (MIC > 2 mg/L) [34]. Mechanism for this resistance is proposed to be due to amino-acid alterations in the ceftaroline-binding site of PBP-2a [34]. The first ceftaroline-resistant *S. aureus* isolate was reported in the United States in 2014 [35].

CONCLUSION

Severe MRSA infections are an ongoing problem with high rates of clinical failure with standard antibiotic therapy, resulting in morbidity and mortality. A growing body of published reports document clinical success of ceftaroline in the treatment of serious MRSA infections, including IE, bacteremia, orthopedic infections, CNS infections, and nosocomial pneumonia. The combination of ceftaroline with daptomycin has also been used with increasing frequency with reports of clinical success for difficult cases of MRSA bacteremia. However, as previously mentioned, response rates are difficult to interpret because studies are primarily case series and anecdotes that evaluate combination therapy without comparator arms, and we acknowledge these limitations. Ceftaroline is generally well tolerated, with a toxicity profile like that of other cephalosporins but with a notably high rate of neutropenia during longer courses of therapy.

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