Ceftaroline, an update

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Abstract

Objective: The objective of this review is to describe the outcomes of patients treated with ceftaroline in non-Food and Drug Administration (FDA) approved indications in pediatric or adult populations with infections caused by MRSA. Data sources: A systematic overview was conducted by searching PubMed, Medline, and The Cochrane Library up to October 2017. Study selection and data extraction: All English-language clinical trials and case reports related to the efficacy of ceftaroline in new, not yet approved FDA indications in methicillin-resistant Staphylococcus aureus infections in pediatric or adult populations. Data synthesis: In the case of methicillin-resistant Staphylococcus aureus (MRSA) infections, three different randomized studies in pediatric patients showed effectiveness of ceftaroline. When used in the case of adult populations with MRSA bacteremia, a small trial of 16 patients showed 50% clinical success in patients with acute bacterial skin and skin structure infections versus 63% clinical success in patients with community-acquired bacterial pneumonia, respectively. Another case series of 6 refractory case reports showed 50% clinical success of ceftaroline in patients with MRSA bacteremia. Conclusions: Although there are few case reports and limited data to date, ceftaroline fosamil should continue to be studied as an alternative therapy in different type of infections.
Introduction

Ceftaroline is a novel cephalosporin, given to patients by intravenous (IV) infusion. It is the active form of ceftaroline fosamil, a bactericidal antibiotic with Gram-positive and -negative coverage. Ceftaroline fosamil exists as Teflaro® (Forest Laboratories, Inc., New York, USA) in the United States. It was approved by the FDA in 2010 for adults and 2016 for children older than 2 months for two indications: complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP). Ceftaroline showed superior efficacy to ceftriaxone in adults with CAP in two phase-3 trials: FOCUS1 and FOCUS 2. They were multi-centered, multinational randomized trials which evaluated the safety and efficacy of 600 mg intravenous (IV) every 12 hours ceftaroline fosamil compared to ceftriaxone 1g IV every 24 hours for 5 to 7 days for treatment of hospitalized CAP patients but did not include patients with MRSA infections. In this update, we will discuss new applications of ceftaroline in specific populations based on new case reports, clinical trials and other observational studies reported in literature.

Data sources

A systematic overview was conducted by searching PubMed, Medline, The Cochrane Library and other reliable outlets published up to October 2017. The search terms used include ceftaroline, adult methicillin resistant Staphylococcus aureus, pediatrics, pediatric methicillin resistant Staphylococcus aureus, bacteremia, antimicrobial activity. Six of the largest controlled studies were included in this update, in addition to a case series reported. The studies selected in this review are the ones that provide data for the use of ceftaroline in refractory patients with MRSA infections.

Chemistry/mode of action/pharmacology
Modification of the fourth-generation cephalosporin cefozopran led to ceftaroline. Ceftaroline is described as a "fifth-generation" cephalosporin due to its reported broader activity against Gram-positive bacteria such as MRSA. Ceftaroline exerts a bactericidal effect through inhibition of the bacterial cell wall synthesis. This is achieved through its binding to the penicillin-binding proteins (PBPs), including PBP2a (which confers resistance to methicillin-resistant S. aureus (MRSA)) and PBP2x (which confers resistance to penicillin-resistant S. pneumoniae). Ceftaroline causes a conformational change in PBP2a which allows binding to the active site of the protein. The activity of ceftaroline against MRSA is due to its 1,3-thiazole ring on the 3rd position of the cephalosporin and the oxime in the acyl group attached to the 7th position of the cephalosporin (Figure 1). The ability to penetrate Gram-negative bacteria is due to the 1,2,4-thiadiazole ring off of the 7th position of the cephalosporin. To increase water solubility, a phosphono-group was added, leading to the prodrug ceftaroline fosamil in the form of acetate. The active form ceftaroline has a bicyclic ring with four-member beta-lactam ring fused to a six membered cephem ring (Figure 1).

Figure 1: Structure-activity relationships for ceftaroline.
In vitro antimicrobial activity of ceftaroline against Staphylococcus aureus:

In a study of pediatric patients with acute bacterial skin and skin-structure infections (ABSSSIs), the minimum inhibitory concentration (MIC) range of ceftaroline against Staphylococcus aureus was 0.06 - 1 mg/L, while against methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-sensitive Staphylococcus aureus (MSSA) the ranges were 0.5 - 1 mg/L and 0.06 - 0.5 mg/L, respectively. In the AWARE program in the United States, the MIC against MRSA was 0.5 µg/mL. Meanwhile, in Europe, South Africa and the Asia-Pacific region, the MIC values were both 1 µg/mL.

In an in vivo study in rabbits’ endocarditis models, the MIC of ceftaroline in one study against MRSA and heterogenous glycopeptide-intermediate S. aureus (hGISA) was 1 mg/L and 2 mg/L, respectively. In another study, the MICs of ceftaroline against methicillin-susceptible S. aureus (MSSA), MRSA and glycopeptide-intermediate S. aureus (GISA) were 0.5 mg/L, 1 mg/L and 1 mg/L, respectively.

Other resistant bacterial strains, including heteroresistant vancomycin-intermediate S. aureus (hVISA), vancomycin-intermediate S. aureus (VISA) and vancomycin-resistant S. aureus (VRSA) are also susceptible to ceftaroline, with MIC ranges of ≤0.25 – 4 mg/L.

Ceftaroline has shown to have activity against both Gram-positive organisms, such as S. pneumoniae and S. aureus, as well as Gram-negative bacteria such as Haemophilus influenza, Klebsiella pneumoniae, Escherichia coli and Moraxella catarrhalis.
Specific populations:

**Pediatrics:**

Ceftaroline fosamil was approved by the FDA in 2016 for pediatric patients from 2 months till 18 years of age to treat two specific indications: ABSSSI (for MSSA and MRSA pathogens) and CABP (for only MSSA).

**MRSA: case series and review of the literature**

Recent analyses have shown that community-acquired MRSA (CA-MRSA) first occurred in children in the United States instead of adults.\(^{23}\) Ceftaroline has shown *in vitro* activity against MSSA and MRSA bacterial isolates.\(^{28}\) A systematic overview was conducted by searching PubMed, Medline, The Cochrane Library and other reliable outlets up to October 2017. Reports of pediatric patients with MRSA infections are documented but no clinical trials exist yet.

**Pediatrics MRSA:**

The treatment of CA-MRSA infections has undergone many changes in the empiric choice of antibiotics mainly because of the scarcity of pediatric clinical trials.\(^{24}\) Many questions arise regarding which combination leads to a faster cure clinically and microbiologically; should the antibiotics be given as a combination? Are new antibiotics more efficient in refractory cases even though there are no sufficient trials to prove it?\(^{25}\) In a multicentered, randomized, observer-blinded study comparing the safety and effectiveness of ceftaroline with ceftriaxone and vancomycin in pediatrics, 4 patients diagnosed with MRSA infections were enrolled in the study\(^{26}\) and were given ceftaroline. Favorable microbiological outcome was shown during treatment as well as clinical cure was achieved at day 4 of the study at the TOC (test of cure) visit. Another study of pediatric patients with community-acquired bacterial pneumonia (CABP)
was randomized in an observer blinded study to receive either intravenous ceftaroline fosamil or ceftriaxone (with an option to switch to oral treatment) for a duration of 5-14 days. The ceftaroline fosamil dosage was adjusted based on the patient’s age and weight. Three documented *S. aureus* infections, including one MRSA infection, were successfully treated in the study. The study found ceftaroline fosamil to have similar safety, efficacy and tolerability to the comparator drug. Few adverse effects were reported in the study. In another multicentered, randomized, observer-blinded study in pediatric patients with complicated CABP, patients ranging from two months to 17 years of age were treated with intravenous ceftriaxone plus vancomycin or ceftaroline fosamil. Ceftaroline fosamil or comparator were given for greater than or equal to three days of treatment with an option to switch to oral treatment in or after day 4. IV study drug or the combination IV study drug plus oral drug was then administered for 5-21 days. Ceftaroline fosamil was again found to display similar clinical response rates and tolerability as the comparator. Treatment Emergent Adverse Events (TEAEs) were mostly mild to moderate and the proportion of ceftaroline fosamil patients reporting TEAEs (40%) was lower than that of the comparator group (80%).

*Adults MRSA bacteremia (MRSAB):*

No randomized controlled trials exist for the case of treatment of MRSA bacteremia with ceftaroline. Results from the 2010 AWARE study, which evaluated antimicrobial resistance, showed that ceftaroline has high activity against MRSA isolates collected from different medical centers in the US.\textsuperscript{16} The 2011 Infectious Diseases Society of America (IDSA) MRSA guidelines recommend vancomycin or daptomycin as a treatment of choice for both complicated and uncomplicated MRSAB.\textsuperscript{27,28} IDSA recommends assessment of patients after 7 days of therapy. No agent has proven to be superior to vancomycin or daptomycin but data of different case
reports or small subgroups of clinical trials prove the basis for alternate agents in case of persistent MRSAB; which includes quinupristin-dalfopristin, trimethoprim-sulfamethoxazole, linezolid, and telavancin.\textsuperscript{30,33} In the trial for treatment of \textit{Staphylococcus aureus} bacteremia (SAB) secondary to ABSSSI and CABP, ceftaroline treatment was assessed. Out of the 48 patients with SAB secondary to ABSSSI enrolled, 32 patients were diagnosed with MRSA infections and out of 27 patients with SAB secondary to CABP, 16 patients were diagnosed with MRSA infections.\textsuperscript{29} Clinical success rates of SAB with MRSA infections secondary to ABSSSI and CABP was 50\% (8/16) and 63\% (10/16), respectively. A case series of 6 patients who received ceftaroline as salvage therapy for MRSAB and other concomitant infections like uveitis, osteomyelitis, septic thrombophlebitis and endocarditis, was reported.\textsuperscript{30} The patients had already had treatment with either vancomycin or daptomycin then were switched to ceftaroline for 14 days as a median therapy. Out of the 6 patients, 5 (83\%) achieved clinical success with ceftaroline and resolution of MRSAB. Another case series included 6 patients with MRSAB and concomitant endocarditis or deep-seated infections.\textsuperscript{31} After failing to respond to vancomycin, relapsing after treatment administration or experiencing therapy-limiting side effects, the patients were switched to ceftaroline. Out of the 6 patients treated with ceftaroline, 3 (50\%) showed clinical success defined as resolution of all signs and symptoms of infection or improvement in a way where antibiotic therapy is not necessary. The same criteria applied to a study conducted by Polenakovich, where 31 patients with MRSAB were involved, including 9 of them who had endocarditis also. The patients received 5 days of therapy with different antibiotics then were switched to ceftaroline; 23 patients (74\%) showed clinical success.\textsuperscript{32} The largest series was a retrospective observational multicentered study that included 527 patients. 123 patients were
diagnosed with MRSAB that received antibiotics therapy before being switched to ceftaroline. 101 patients showed clinical success (79%).

**Dosing:**

Cefaroline is indicated for children aged more than 2 months old with infections including CABP and ASSSI. First, the CABP infection should be caused by susceptible isolates of Gram-positive and -negative bacteria which include *Streptococcus pneumoniae* (with concurrent bacteremia cases), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Klebsiella oxytoca*. Second, the ABSSSI infection should be caused by susceptible isolates of Gram-positive and -negative bacteria which include *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. (Table 1)

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<th>CABP</th>
<th>Age</th>
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<tr>
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<td>2 months to &lt;2 years</td>
<td>8 mg/kg IV q8hr x 5-14 days</td>
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<td></td>
<td>≥2 years to &lt;18 years (≤33 kg)</td>
<td>12 mg/kg IV q8hr x 5-14 days</td>
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<td>400 mg q8hr OR 600 mg q12hr IV x 5-14 days</td>
</tr>
<tr>
<td></td>
<td>≥18 year</td>
<td>600 mg IV q12hr; infuse over 5-60 minutes for 5-7 days</td>
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<table>
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<th>ABSSSI</th>
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<td>8 mg/kg IV q8hr x5-14 days</td>
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**Table 1: Proposed doses for the use of ceftaroline.**

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It is worthy to note that in the randomized prospective study of Kaplan et al\textsuperscript{15} and Bradley et al\textsuperscript{14} the pediatric patients were given ceftaroline doses based on the pediatric population pharmacokinetic modeling and consistent with what is indicated in the table above. Whereas the doses used for the pediatric patients with CABP in the Bradley et al\textsuperscript{31} clinical trial\textsuperscript{31} is the IV infusion of ceftaroline over 120 min every 8 hours at a dose of 15mg/kg and 10 mg/kg for patients more than 6 months old. This regimen is considered higher than the doses proposed for the use of ceftaroline.

\textit{Safety:}

In the CANVAS\textsuperscript{35} program, the most common adverse effects reported were nausea (5.9%), headache (5.2%), diarrhea (4.9%), pruritus (3.5%) and rash (3.2%).\textsuperscript{36} In the FOCUS program, the most common adverse effects reported were diarrhea (4.2%), headache (3.4%) and insomnia (3.1%).\textsuperscript{37} In both programs, the development of allergic reactions to ceftaroline led to its discontinuation. Serious adverse events occurred in 11\% of patients in the FOCUS program and 4\% of patients in the CANVAS program; however, >90\% were deemed to be unrelated to ceftaroline.\textsuperscript{41,42}

\textbf{Conclusion}

MRSA is known to cause a variety of infectious problems including ABSSSIs, and skin and soft tissue infections (SSTIs) in adults and children. Alternative medications must be developed to treat patients who fail treatment with traditional therapies such as vancomycin and clindamycin. Although there are few case reports and limited data to date, ceftaroline fosamil should continue to be studied as an alternative therapy for pediatric patients with MRSA. Ceftaroline fosamil is a broad-spectrum cephalosporin antibiotic that has been used to treat against MRSA in refractory
cases. Ceftaroline fosamil, has shown to be safe, well tolerated and efficacious among children and adults, including those with MRSA, who are resistant or require an alternative antibiotic to common treatments. Treatment of patients with VRSA infections with ceftaroline should also be considered as an option to be reported and documented in literature.
Key points:

- Evidence suggests that ceftaroline used for the treatment of MRSA has shown to be successful in terms of clinical cure.
- There are still few limited data to date regarding the efficacy of ceftaroline alone or when compared to other antibiotics for the treatment of MRSA like quinupristin-dalfopristin, trimethoprim-sulfamethoxazole, linezolid, and telavancin.
- Evidence suggests that ceftaroline has shown to be safe when administered in both adults and pediatrics.
References


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34. www.fda.gov/medwatch.
