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REVIEW ARTICLE

Current Clinical Trials on the Use of Ceftaroline in the Pediatric Population

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Abstract The rate of antibiotic resistance in children continues to rise requiring the use of new antibiotics. Ceftaroline fosamil, a newer-generation cephalosporin, was recently approved for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia in children aged >2 months. Ceftaroline provides coverage against staphylococcal and streptococcal infections, including methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. Pediatric dosing differs from adult dosing, but it maintains a similar pharmacokinetic profile and offers similar efficacy in terms of time above the minimum inhibitory concentration as compared to the adult population. The clinical safety and efficacy of this antibiotic has been assessed in three pediatric clinical trials that led to its approval by the US Food and Drug Administration, and each trial is described within this review. This article will also discuss the ongoing trials assessing the possibility of expanding the indications of this antibiotic to late-onset sepsis, meningitis and osteomyelitis in the pediatric population.

Key Points

Ceftaroline was recently approved for the treatment of acute bacterial skin and skin structure infection and community-acquired bacterial pneumonia in children aged >2 months.

Ceftaroline provides coverage against staphylococcal and streptococcal infections, including methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*.

More studies are ongoing looking into broadening the indications of ceftaroline to late-onset sepsis, meningitis and osteomyelitis in the pediatric population.

1 Introduction

Antibiotic resistance represents a growing cause of morbidity and mortality in health care, and this issue is further complicated in pediatric patients. Few antimicrobial agents have received approval from the US Food and Drug Administration (FDA) to treat resistant pathogens in children while the rate of resistance for Gram-positive bacteria increases. In some areas, methicillin-resistant *Staphylococcus aureus* (MRSA) has reached 60–70% of all pediatric staphylococcal infections in the community [1]. Similarly, the prevalence of penicillin-resistant *Streptococcus pneumoniae* (PRSP) remains a significant burden despite vaccination efforts [2].

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Children are prone to bacterial skin infection like cellulitis due to their time in close contact at daycare and school. Adolescents participating in sports teams have seen an increase in MRSA-related acute bacterial skin and skin structure infections (ABSSSIs). Likewise, 3 million children develop community-acquired bacterial pneumonia (CABP) each year with more than 150,000 requiring hospitalization and most of these infections are caused by MRSA and PRSP [3]. Intravenous therapy for MRSA infections in pediatrics remains limited to vancomycin, clindamycin, and linezolid despite safety, susceptibility and cost concerns [4]. Ceftaroline is a newer antibiotic approved to treat adults and pediatrics aged >2 months with ABSSSI and CABP [5]. At this time, literature on the use of ceftaroline in children is scarce. This article will review current literature, describe ongoing studies and recommend the proper use of this antibiotic in the pediatric population.

2 Methods of Literature Search

MEDLINE/PubMed searches were performed by the authors to identify all literature published to date since 2012 that addressed ceftaroline use in the pediatric population. The searches were done on PubMed (http://www.ncbi.nlm.nih.gov). One set was created using the Medical Subject Heading (MeSH) terms "pediatric" OR "ceftaroline". Combining the two sets with the Boolean "AND" function yield 21 citations. We included article types consisting of only clinical trials, journal articles, and reviews. We limited our search to articles that had full text and excluded abstracts only, case reports, incomplete reports, and letters from our review. Also, we performed searches on ClinicalTrials.gov (http://www.clinicaltrials.gov) with the search terms "ceftaroline" AND "children", which yielded 7 relevant ongoing and completed studies.

3 Pharmacology

3.1 Mechanism of Action

Ceftaroline, available as the prodrug ceftaroline fosamil, is a newer-generation cephalosporin. As a beta-lactam antibiotic, ceftaroline targets penicillin-binding proteins (PBPs) inhibiting bacterial cell wall formation and leading to its bactericidal effects. In response to previous beta-lactam agents, pathogens develop resistance mechanisms primarily through mutations of the PBPs. MRSA possesses the PBP-2a variant and penicillin-resistant *S. pneumoniae* (PRSP) produces a PBP-2× variant. These alterations prevent the binding of most beta-lactam agents, conferring resistance to the class. However, ceftaroline's structure allows for greater binding affinity to PBP-2a and PBP-2×, thus maintaining the agent's activity against MRSA, PRSP and other multi-drug resistant pathogens [6].

The spectrum of activity for ceftaroline is similar to other cephalosporins. Ceftaroline has good activity against most Gram-positive bacteria, such as *Streptococcus* (including PRSP) and *Staphylococcus* (including MRSA). Gram-negative coverage of ceftaroline includes *Escherichia coli*, *Klebsiella*, and *Haemophilus influenzae*. Like other cephalosporins, ceftaroline lacks coverage against enterococcal strains. Other pathogens with poor coverage from this antibiotic include organisms with extended-spectrum beta-lactamase, carbapenem-resistant *Klebsiella*, *Bacteriosides* and *Prevotella*. Of note, ceftaroline also does not provide coverage against pseudomonal infections [6, 7] (Table 1).

Based on its mechanism of action and spectrum of activity, ceftaroline fosamil was approved by the FDA in 2010 for the treatment of adults with ABSSSI and CABP. In 2016, the FDA extended the indication of ceftaroline for the treatment of children between the ages of 2 months and 18 years with these same two indications [5]. The approval was based on three clinical studies, two in CABP and one in ABSSSI, along with pharmacokinetic data [8–12]. Other trials are currently ongoing to determine the possibility of further expanding ceftaroline to treat other conditions, such as bacterial meningitis [13–15].

3.2 Pharmacokinetics

Few kinetic studies include pediatric patients; therefore, most pharmacokinetic data regarding ceftaroline come from the adult population. Adults receive a 600-mg dose through intravenous infusion over 60 min every 12 h. Upon infusion, ceftaroline, available in the form ceftaroline fosamil, must be activated via dephosphorylation. Ceftaroline reaches a maximum concentration (C_{max}) of 21 mcg/mL and an area under the curve (AUC) of 56 μg·h/mL. The elimination half-life is 2.7 h with 88% of the dose excreted through the urine. Renal elimination requires adjustments of this antibiotic in patients with a creatinine clearance (CrCl) less than 50 mL/min. Only 2% of the ceftaroline dose is metabolized into an inactive metabolite, M-1. Ceftaroline does not act as a cytochrome P450 substrate, nor does it inhibit or induce any liver enzymes, leading to its limited drug–drug interactions [6].

A single-dose pharmacokinetic trial analyzed the concentrations and safety of ceftaroline in pediatrics [11]. This phase 1 study included 9 children between the ages of 12–17 years with a body-mass index (BMI) less than 30 kg/m^2 who were hospitalized for suspected infection. Patients with a known hypersensitivity to beta-lactam

Table 1 Spectrum of activity for ceftaroline [5–7]

Good activity		Poor activity/ineffective
Gram-positive bacteria	**$MIC_{50/90}$ (mcg/mL)**	*Enterococcus*
S. pneumoniae	≤0.015/0.12	ESBL *Klebsiella*
Pen-R (PRSP)	0.12/0.25	Carbapenem-resistant *Klebsiella*
CTX- R	0.25/0.5	*Bacteriosides*
S. aureus	0.25/1	*Prevotella*
MSSA	0.25/0.25	*Pseudomonas*
MRSA	1/1	
Gram-negative bacteria		
E. coli	0.12/0.5	
Klebsiella	0.12/0.5	
H. influenza	≤0.015/≤0.015	
β-lactamase negative	≤0.015/≤0.015	
β-lactamase positive	≤0.015/0.03	

CTX-R ceftriaxone resistant, ESBL extended-spectrum beta-lactamase, *$MIC_{50/90}$* mean inhibitory concentration of 50/90% of isolates, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-sensitive *S. aureus, PEN-R* penicillin resistant, *PRSP* penicillin-resistant *S. pneumoniae*

antibiotics, history of seizures, or who were critically ill or unstable were excluded from the study. Patients received a single dose of ceftaroline 8 mg/kg (maximum 600 mg/dose) intravenously over 60 min. The primary outcome identified a C_{max} of 15 ± 6 mcg/mL, which is similar to that in adults. The trial also assessed treatment-emergent adverse events (TEAEs) and found each patient who received a dose experienced at least one TEAE. One serious adverse event was a pathological fracture. Other adverse events included extrasystoles, vomiting, constipation, extravasation, prolonged QT, arthralgia, and nasal dryness [11]. However, it remains unknown if these events were related to ceftaroline or other causes. For example, ceftaroline has not been shown to have a significant effect on QTc interval in doses up to 1500 mg in one adult study [16]. With the administration of a single-dose, this trial provided the first information in regards to the pharmacokinetics of ceftaroline in children between 12 and 17 years of age. However, the exclusion criteria limits applicability of these data to obese children and critically ill patients.

A second single-dose trial enrolled 53 children under the age of 12 years hospitalized for infection requiring systemic antibiotic therapy [12]. Patients with hypersensitivity to beta-lactam agents, renal impairment or seizure disorder were excluded. This phase 4 trial was designed to determine the single-dose pharmacokinetic profile in younger patients. The subjects received a one-time dose of 15 mg/kg up to a maximum dose of 600 mg. The plasma concentration of ceftaroline fosamil and its metabolites were collected over a 5-day period to produce a plasma concentration–time profile. Additionally, investigators monitored the patients for adverse events to determine safety and tolerability. The trial was completed in 2013, but no results have been published thus far [12]. While this study addressed the pharmacokinetics of children under the age of 12 years, the investigators used a dose that was greater than the current FDA-recommended 8–12 mg/kg for this age group, which could have potentially confounded the safety data. As with the previous trial, patients with a hypersensitivity to other beta-lactam agents were excluded limiting its external validity.

A population pharmacokinetic study combined the results of 5 pediatric studies that included 305 children from birth to the age of 18 years and compared them to known adult data [17]. The studies utilized standardized dosing of 8 mg/kg every 8 h for children aged ≥2 months and <2 years. Children older than 2 years received a dose of 12 mg/kg every 8 h up to a weight of 33 kg. Older children >33 kg could receive 400 mg every 8 h or 600 mg every 12 h, the recommended dose by the European Medicines Agency (EMA) [18]. For comparison, the adult dose is 600 mg every 12 h. The model aimed to predict the percent of children that would maintain concentration above the minimum inhibitory concentration (MIC). Based on the dosing regimens, pediatric patients of all ages maintained a concentration greater than an MIC of 1 mcg/mL more than 75% of the time, while adults only remained above the MIC 64% of the time. The study determined that every 8-h dosing would produce a concentration above an MIC of 1 mcg/mL at least 44% of the time in >99% of patients as well as >94% of patients will achieve a concentration greater than an MIC of 2 mcg/mL for more than 36% of the dosing interval. Meanwhile, the 12-h dosing alternative for older children would maintain concentrations above the MIC of 1 mcg/mL 44% of the

time in >97% of children and above an MIC of 2 mcg/mL for 36% of the time in >90% of children. Compared to adults, children aged between 2 months and 2 years demonstrated a similar median C_{max} of 19 mcg/mL (vs. median C_{max} of 21 mcg/mL in adults), but a higher median AUC of greater than 110 μg·h/mL, up to 134 μg·h/mL in children less than 6 months old, was observed (vs. median AUC of 97.3 μg·h/mL in adults). Children older than 2 years of age yielded results greater than their adult counterparts. The pediatric median C_{max} for this age group was greater than 27 mcg/mL, except for those children 12–18 years old receiving antibiotic doses of 12 mg/kg every 8 h (median C_{max} = 19.7 mcg/mL). Children between 12 and 18 years of age who received 600 mg every 12 h had a median C_{max} of 28.6 mcg/mL. All doses for children over 2 years of age produced a median AUC greater than 120 μg·h/mL, up to 157 μg·h/mL in children between the ages of 6–12 years [17]. No elimination half-life was calculated for the pediatric patients. Based on this model, the authors concluded that the tested dosing regimen would produce similar drug exposure to adult dosing for the treatment of *S. aureus* and *S. pneumoniae*. By combining the results of several studies and including the maximum doses recommended in both the USA and Europe, the authors were able to produce a more complete pharmacokinetic model of ceftaroline in pediatric patients. This study, however, did not assess the patients' renal function, which could have affected the results.

4 Clinical Trials

4.1 Community-Acquired Bacterial Pneumonia

The use of ceftaroline in pediatric patients was approved for CABP based on two multi-center trials against active comparators [8, 9]. One trial compared ceftaroline to ceftriaxone [8], while the other used ceftriaxone plus vancomycin [9]. In both trials, the primary objective addressed the safety and tolerability of ceftaroline, while the secondary objective determined clinical response [8, 9].

The first of these trials included 160 children between the ages of 2 months and 17 years with a clinical case of CABP requiring hospitalization and intravenous therapy [8]. The trial excluded patients with known hypersensitivity to any beta-lactam agents and who had received more than 24 h of antibiotics and had documented pathogens (including MRSA) resistant to ceftriaxone. Patients in the ceftaroline group received a dose of 12 mg/kg (up to 400 mg/dose) infused over 60 min every 8 h. Patients aged between 2 and 6 months received 8 mg/kg per dose. The comparator group received ceftriaxone at 75 mg/kg/d divided into 2 doses. After 3 days of IV treatment, patients could switch to oral amoxicillin/clavulanate for the remainder of the treatment course [8].

For the primary outcome, patients tolerated ceftaroline at the same rate as ceftriaxone. Forty-five percent of patients in the ceftaroline group experienced a TEAE compared to 46.2% in the ceftriaxone group. Only 9.9% of ceftaroline TEAEs were related to the study drug, similar to 7.7% of ceftriaxone TEAEs. The most common TEAEs were diarrhea, vomiting, pyrexia, thrombocytosis and otitis media. In the secondary outcome, both groups experienced similar rates of clinical response (69.2 vs. 66.7% at Day 4) and clinical cure rate at the end of treatment (91.6 vs. 88.9%). Therefore, the investigators concluded that ceftaroline was a well-tolerated potential treatment for CABP in pediatric patients [8].

While this trial demonstrated similar safety profile between ceftaroline and ceftriaxone, its major limitation is the exclusion of patients with confirmed or suspected MRSA-related CABP and patients in the intensive care unit (ICU). Thus, the results of this trial are limited to non-critically ill patients without suspicion of MRSA infection nor any history of beta-lactam hypersensitivity. Also, because the primary outcome focused only on safety and tolerability, this trail was not powered to determine efficacy.

The primary advantage of ceftaroline is the ability to treat infections caused by drug-resistant pathogens, such as MRSA and PRSP, but the previous study failed to include patients with confirmed or suspected MRSA-related CABP. A smaller, but non-powered trial compared ceftaroline to ceftriaxone with vancomycin in 38 children between the ages of 2 months and 18 years with clinical CABP requiring hospitalization [9]. Patients were excluded if they had known hypersensitivity to any beta-lactam agents and who had received more than 24 h of antibiotics or had a history of seizures or meningitis. Randomized patients to the ceftaroline group received a dose of 15 mg/kg (max 600 mg/dose) over 120 min every 8 h. Infants between 2 and 6 months of age received smaller doses of 10 mg/kg. The comparison group received ceftriaxone 75 mg/kg/day in divided doses with empiric vancomycin dosed at 15 mg/kg every 6 h. After 4 days, vancomycin could be discontinued if MRSA or PRSP were not identified. Patients could switch to an oral agent, including amoxicillin/clavulanate, clindamycin or linezolid based on microbial sensitivity testing [9].

TEAEs occurred in 40% of patients on ceftaroline and 80% of the comparison group. The most common TEAEs were anemia, pruritus, vomiting and upper respiratory infection. No difference was found between the groups in terms of clinical cure at the end of treatment (82.8 vs. 77.8%; difference 5%, 95% CI −19.9 to 40.3) or clinical response at day 4 (51.7 vs. 66.7%; difference −14.7%,

95% CI −44.6 to 22.0). While this trial included MRSA and PRSP infections, vancomycin and ceftaroline were continued for at least 4 days regardless of sensitivities. Additionally, the ceftaroline patients received a dose higher than the standard FDA-recommendation, which might have confounded the TEAEs and clinical efficacy. Despite the small sample size and primary focus on tolerability, the authors determined that ceftaroline is a viable option for the treatment of pediatric CABP compared to ceftriaxone plus vancomycin [9].

4.2 Acute Bacterial Skin and Skin Structure Infection

Approval of ceftaroline for ABSSSI was based on a phase 2/3, multicenter, randomized, active-control trial of 169 children aged 2 months to 17 years [10]. To be included in the study, patients required a diagnosis of complicated ABSSSI, including abscesses, wound infections and cellulitis, requiring hospitalization and intravenous antibiotics. Subjects could not have received more than 24 h of antibiotics before randomizations or have a diagnosis of meningitis. The study excluded patients with a previous history of hypersensitivity to beta-lactam antibiotics, vancomycin or aztreonam, as well as a history of seizures [10].

Patients in the ceftaroline group received 12 mg/kg every 8 h, up to 400 mg/dose for patients greater than 33 kg. Patients between 2 and 6 months were given 8 mg/kg. The active controls were given vancomycin 15 mg/kg every 6 h or cefazolin 75 mg/kg/day divided into three doses. Aztreonam was added if Gram-negative coverage was needed. After 4 days, patients could switch to an oral agent, including cephalexin 25 mg/kg every 6 h, clindamycin 10 mg/kg every 8 h, or linezolid 10 mg/kg every 8 h (or 600 mg every 12 h for patients over 12 years of age). Selection of the oral agent was based on MRSA susceptibility [10].

In this trial, the primary outcome assessed the safety and tolerability of ceftaroline. No difference was observed between the ceftaroline group and the comparator groups in terms of TEAE. Forty-eight percent of ceftaroline patients experienced one or more TEAEs compared to 43% in the vancomycin or cefazolin groups. The most common adverse events included diarrhea (8% in the ceftaroline group vs. 15% in the comparator group), rash (8 vs. 4%), vomiting (7 vs. 15%), and pruritus (1 vs. 6%), respectively. The secondary outcome did not find any difference between the groups in terms of clinical response at day 3 (80.4 vs. 75%; difference 5.4%, 95% CI −10.7 to 13.9) and clinical cure rate at the end of treatment (96.3 vs. 88.5%; difference 7.8%, 95% CI −0.3 to 196). The microbiological eradication was also not statistically different between the treatment groups (94.2 vs. 81.8%; difference 12.4%, 95% CI −2.1 to 33.6), except for a potential difference in patients with MRSA (88.9 vs. 57.1%).

This study demonstrated similarity in the safety of ceftaroline to vancomycin; however, it was again not powered to assess the efficacy of ceftaroline despite the positive results. Also, this study did not provide any evidence on the safety and efficacy of ceftaroline in specialized population such as immunocompromised patients or those with renal dysfunction. Considering the positive results and the potential limitations, the authors concluded that ceftaroline was a safe option as an intravenous therapy for the first 3 days of treating ABSSSIs in the pediatric population [10].

4.3 Ongoing Studies

Based on previous successful studies of ceftaroline for ABSSSI and CABP, several clinical trials are currently recruiting pediatric patients for other infectious diseases since ceftaroline activity against drug-resistant organisms makes it a possible treatment option for sepsis, meningitis, and osteomyelitis [13–15].

One current phase 2/3, open-label study assesses the use of ceftaroline in pediatric patients with late-onset sepsis [13]. Investigators estimate that a sample size of 24 children up to 59 days old (including gestational age ≥34 weeks) will be recruited in this study. Subjects with a history of seizure and hypersensitivity to beta-lactam antibiotics, as well as renal impairment, human immunodeficiency virus, and meningitis will be excluded. The primary outcome will address safety and tolerability, while the secondary objectives will assess the concentration of ceftaroline and M-1 in the plasma and cerebrospinal fluid (CSF). It will also evaluate clinical efficacy 14 days following treatment with this antibiotic. The inclusion of children less than 60 days old addresses an important potential population, but it fails to study more premature children (i.e. <34 weeks of gestational age) or those with renal impairment or who are immunocompromised. This study is currently recruiting patients; no results have been posted [13].

Another phase 1, open-label study will measure the concentration of ceftaroline in the CSF [14]. The investigators are recruiting 12 patients between the ages of 6 months to 17 years with ventriculitis due to bacterial infection and an external ventriculostomy drain in place. Patients with known allergy to beta-lactam antibiotics and renal impairment will be excluded. Randomized patients will receive a single dose of ceftaroline and a pharmacokinetic profile will be based on three samples of plasma and CSF over 8 h after administration. The aim of the study is to determine the amount of ceftaroline from a single dose that will cross the blood–brain barrier into the

CSF for the purpose of treating central nervous system infections caused by drug-resistant pathogens. The inclusion of patients with a ventriculostomy drain allows access to CSF without additional intrusion or discomfort. Determining the pharmacokinetic profile of ceftaroline in the CSF may expand the indications to include meningitis. However, this study is only recruiting a maximum of 12 patients with a wide range of ages and lacks assessment of children less than 6 months old. Similar to the previous study, this phase 1 study is currently recruiting patients; no results have been posted thus far [14].

As ceftaroline possesses activity against *S. aureus* pathogens including MRSA, a phase 1/2, open-label study will follow 18 patients between 1 and 17 years of age with hematogenously acquired *S. aureus* osteomyelitis of a large bone [15]. Exclusion criteria will limit patients with multiple bone infections, disseminated infection, renal dysfunction, and hypersensitivity to beta-lactam antibiotics. Ceftaroline will be dosed at 15 mg/kg (maximum 600 mg/dose) over 120 min every 8 h. Children less than 2 years old will receive 10 mg/kg over 120 min every 8 h. The investigators will primarily assess the safety and tolerability of this antibiotic in terms of TEAEs, serious adverse events, deaths, and discontinuations. Secondary outcomes include clinical response at the end of the intravenous treatment, clinical outcome at the end of total therapy, clinical outcome 1 year after therapy, and the proportion of patients with ceftaroline concentrations greater than 1 mcg/mL for more than 60% of the administration of the antibiotic. While the study includes osteomyelitis, patients with multiple bone infections or bacteremia have been excluded. Likewise, no information will be gathered regarding patients with renal dysfunction or prior beta-lactam hypersensitivity [15]. The results of all these ongoing studies will surely add to the body of evidence supporting the use of ceftaroline in the pediatric population. Table 2 shows a summary of all the aforementioned studies.

5 Current Clinical Application

At this time, ceftaroline has been approved for the treatment of ABSSSI and CABP in hospitalized pediatric patients requiring intravenous antibiotics. Due to concerns of developing resistance, ceftaroline should be reserved for patients with known or suspected cases of MRSA or PRSP. Yim et al. [20] cautioned that clinical data of ceftaroline in pediatrics are currently limited and recommended diligent antibiotic stewardship to reserve its use for the appropriate populations and infections. With sensitivity testing, clinicians should narrow therapy appropriately if the pathogen is not drug-resistant [6].

Dosing ceftaroline is based on both age and weight. According to the package insert, children between the ages of 2 months to <2 years should receive a lower dose at 8 mg/kg every 8 h. Patients aged ≥2 years should be given 12 mg/kg every 8 h with a maximum dose of 400 mg/dose in patients weighing greater than 33 kg. Alternatively, a 600-mg dose may be given every 12 h. The IV infusion time has been approved between 5 and 60 min, allowing for variation based on circumstances [5]. In general, ceftaroline should be administered over 60 min as a time-dependent antibiotic. Treatment duration spans from 5 to 14 days based on the source of infection and clinical recovery. CABP treatment should last 5–7 days, while ABSSSI treatment should last 5–14 days. As in the clinical trials, conversion to oral antibiotics may be warranted based on clinical progress and microbial sensitivities [5] (Table 3).

Ceftaroline is contraindicated in patients with previous history of hypersensitivity to any cephalosporins as cases of anaphylaxis have occurred [5]. Each of the previously described clinical trials excluded patients with a known hypersensitivity to beta-lactam antibiotics, thus the potential for hypersensitivity due to ceftaroline remains unknown. Cross-reactivity between penicillin and cephalosporin has been documented but remains low, especially for higher-generation agents [19]. Patients with penicillin allergy who receive ceftaroline should be closely monitored. Clinicians should monitor for drug-induced hemolytic anemia as positive direct Coomb's test was observed in 17% of ceftaroline patients compared to 3% of ceftriaxone patients in a pediatric CABP trial [8]. If such adverse event is suspected, ceftaroline should be discontinued. Pediatric patients also have experienced diarrhea, rash, vomiting, pyrexia and nausea while on this antibiotic [5].

Because ceftaroline undergoes renal clearance, it is recommended to reduce the dose based on renal function in adults. However, pediatric studies excluded patients with renal dysfunction, so children with an estimated CrCl less than 50 mL/min/1.73 m^2 based on the Schwartz equation should not receive ceftaroline until further studies are performed evaluating safety and efficacy in this special population [5].

Despite standardized FDA dosing guidelines, clarification of appropriate infusion time and dosing based on site of infection, concomitant disease states and renal function should be addressed. For example, the two CABP clinical trials used different doses of ceftaroline fosamil [8, 9]. The trial on MRSA-related CABP used a dosage of 15 mg/kg [9], whereas the other trial dosed ceftaroline at 12 mg/kg, consistent with the dosing recommendations by the FDA. Likewise, an ongoing CSF study assesses both the 15 mg/kg dose and the longer infusion interval of 120 min [14]. The authors of a recent review of ceftaroline use in

Table 2 Summary of clinical trials evaluating the use of ceftaroline in pediatric patients [8–15, 17]

Trial	Population	Intervention	Primary outcome	Secondary outcomes
Pharmacokinetic studies				
Pharmacokinetics of a single dose of ceftaroline in subjects 12–17 years of age receiving antibiotic therapy [11] (NCT00633126)	$n = 9$ Included: ages 12–17 years, BMI $\leq$ 30 kg/m^2, hospitalized for infection Excluded: beta-lactam hypersensitivity, history of seizure, critically ill or unstable	Ceftaroline 8 mg/kg IV over 60 min (max 600 mg/dose) × 1 dose	Plasma concentration $C_{max} = 15 \pm 6$ mcg/mL	Safety and tolerability 1 event each of: fracture (severe), extrasystoles, vomiting, constipation, extravasation, prolonged QT, arthralgia, and nasal dryness
Pharmacokinetics of a single dose of ceftaroline fosamil in children ages birth to younger than 12 years with suspected or confirmed infection [12] (NCT01298843)	$n = 53$ Included: age < 12 years, hospitalized for infection Excluded: beta-lactam hypersensitivity, history of seizure, renal/liver impairment, use of probenecid, or blood transfusion	Ceftaroline 15 mg/kg IV × 1 dose	Concentration–time profile Trial completed; no results reported	Safety and tolerability Trial completed; no results reported
Population PK modeling and target attainment simulations to support dosing of ceftaroline fosamil in pediatric patients with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia [17]	$n = 305$ (from 5 trials)	Ceftaroline (doses included from other clinical trials in this table)	Pharmacokinetic simulation 8 h Dosing interval Conc > MIC 2 mcg/mL 36% OTT in >94% of children Conc > MIC 1 mcg/mL 44% OTT in >99% of children *12 h Dosing Interval* Conc > MIC 2 mcg/mL 36% OTT in >90% of children Conc > MIC 1 mcg/mL 44% OTT in >97% of children	Median pharmacokinetic data (C_{max}, mcg/mL; AUC, μg·h/mL) 2–6 months: C_{max} 19.2; AUC 134 6–12 months: C_{max} 19.6; AUC 120 12–18 months: C_{max} 19.1; AUC 113 18–24 months: C_{max} 18.8; AUC 107 2–6 years: C_{max} 27.1; AUC 144 6–12 years: C_{max} 27.6; AUC 157 12–18 years: C_{max} 28.6; AUC 122 Adults: C_{max} 21; AUC 97.3
Completed clinical trials				
A multicenter, randomized, observer-blinded, active-controlled study evaluating the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline versus ceftriaxone in pediatric subjects with community-acquired bacterial pneumonia requiring hospitalization [8] (NCT01530763)	$n = 161$ Included: ages 2 months to 18 years, hospitalization for CABP Excluded: beta-lactam hypersensitivity, pathogens resistant to either agent, viral infection or non-infectious causes	Ceftaroline 12 mg/kg q8h up to 400 mg/dose (<6 months: 8 mg/kg) Ceftriaxone 75 mg/kg/day divided q12h PO switch considered on or after treatment day #4 Amoxicillin/clavulanate 90 mg/kg/day divided q12h	Safety and tolerability TEAE—45.5 vs. 46.2% SAE—5 vs. 2.6% D/C—1.7 vs. 0%	Clinical efficacy Response at day 4—69.2 vs. 66.7% Cure at end of therapy—91.6 vs. 88.9%

Table 2 continued

Trial	Population	Intervention	Primary outcome	Secondary outcomes
A multicenter, randomized, observer-blinded, active controlled study evaluating the safety, tolerability, pharmacokinetics and efficacy of ceftaroline versus ceftriaxone plus vancomycin in pediatric subjects with complicated community-acquired bacterial pneumonia [9] (NCT01669980)	$n = 40$ Included: ages 2 months to 18 years, hospitalization of complicated CABP Excluded: beta-lactam hypersensitivity, vancomycin allergy, known resistance, non-CABP	Ceftaroline 15 mg/kg q8h up to 600 mg/dose (<6 months: 10 mg/kg) Ceftriaxone 75 mg/kg/day divided q12h + vancomycin 15 mg/kg q6h PO switch considered on or after treatment day #4 Amoxicillin/clavulanate Clindamycin Linezolid	Safety and tolerability TEAE—40 vs. 80% SAE—0 vs. 10% D/C—6.7 vs. 0%	Clinical efficacy Response at day 4—51.7 vs. 66.7% Cure at end of therapy—82.8 vs. 77.8%
A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, efficacy and pharmacokinetics of ceftaroline versus comparator in pediatric subjects with acute bacterial skin and skin structure infections [10] (NCT01400867)	$n = 163$ Included: ages 2 months to 18 years, hospitalization for ABSSSI with measurable margins Excluded: beta-lactam hypersensitivity, aztreonam or vancomycin allergy, uncomplicated ABSSSI, ≥24 h of antibiotics, history of seizures, signs of meningitis	Ceftaroline 12 mg/kg q8h up to 400 mg/dose (<6 months: 8 mg/kg) Vancomycin 15 mg/kg q6h ± aztreonam 30 mg/kg q8h Cefazolin 75 mg/kg/day divided q8h ± aztreonam 30 mg/kg q8h PO switch considered on or after treatment day #4 Cephalexin Clindamycin Linezolid	Safety and tolerability TEAE—48 vs. 43% SAE—1.9 vs. 1.9% D/C—4 vs. 4%	Clinical efficacy Response at day 4—80.4 vs. 75% Cure at end of therapy—96.3 vs. 88.5% Cure (MRSA) at end of therapy—89 vs. 57%
Ongoing clinical trials				
Open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftaroline in neonates and young infants with late-onset sepsis [13] (NCT02424734)	n (estimated) = 24 Including: ages 7–59 days, gestational age ≥34 weeks, clinical sepsis Excluding: beta-lactam hypersensitivity, pathogen resistant to agent, renal impairment, history of seizures, CNS infection	Ceftaroline (dose not known)	Safety and tolerability Currently recruiting No results to report	Clinical efficacy and pharmacokinetics Currently recruiting No results to report
Ceftaroline diffusion into cerebrospinal fluid of children with ventriculitis due to ventriculoperitoneal shunt infections [14] (NCT02600793)	n (estimated) = 12 Including: ages 6 months to 17 years with ventriculitis due to VPS Excluding: beta-lactam hypersensitivity, CrCl < 50 mL/min/1.73 m^2	Ceftaroline × 1 (dose not known)	Pharmacokinetic profile Currently recruiting No results to report	N/A

Table 2 continued

Trial	Population	Intervention	Primary outcome	Secondary outcomes
Phase 1/2 trial of ceftaroline for the treatment of hematogenously acquired *S. aureus* osteomyelitis in children [15] (NCT02335905)	n (estimated) = 18 Including: ages 1–17 years, *S. aureus* osteomyelitis of large bone Excluding: beta-lactam hypersensitivity, >1 bone infected, disseminated infection, CrCl < 50 mL/min/1.73 m^2, neutropenia, thrombocytopenia	Ceftaroline 15 mg/kg q8h up to 600 mg/dose (1–2 years: 10 mg/kg)	Safety and tolerability Currently recruiting No results to report	Clinical efficacy Currently recruiting No results to report

ABSSSI acute bacterial skin and skin structure infection, *AUC* area under the curve, *BMI* body mass index, *CABP* community-acquired bacterial pneumonia, C_{max} maximum concentration, *Conc* concentration, *CrCl* creatinine clearance, *D/C* discontinuation, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *OTT* of the time, *PO* by mouth, *SAE* serious adverse events, *S. aureus Staphylococcus aureus*, *TEAE* treatment-emergent adverse events, *VPS* ventriculoperitoneal shunt

Table 3 Administration recommendations of ceftaroline for pediatric patients with ABSSSI and CABP [5]

Age	Dosing	Infusion time	Treatment duration (days)
2 months to <2 years	8 mg/kg q8h	60 min	ABSSSI = 5–14 days CABP = 5–7 days
≥2 years (≤33 kg)	12 mg/kg q8h		
≥2 years (>33 kg)	400 mg q8h *or* 600 mg q12h		

For pediatric patients with CrCl > 50 mL/min/1.73 m^2, based on the Schwartz equation

ABSSSI acute bacterial skin and skin structure infection, *CABP* community-acquired bacterial pneumonia, *kg* kilogram, *mg* milligram, *q8h* every 8 h, *q12h* every 12 h

pediatrics recommended that the higher dosing regimens used in some trials (i.e. 10 mg/kg every 8 h for children less than 6 months and 15 mg/kg every 8 h up to a maximum of 600 mg per dose) may be necessary for drug-resistant infection [20].

As mentioned earlier, no current studies address the proper dosing of ceftaroline in children with a CrCl less than 50 mL/min/1.73 m^2. Dosage recommendations of this antibiotic in renal dysfunction should be determined for pediatric patients as in the adult population. On the other end, studies are needed to determine if the 400 mg every 8 h (q8h) is a better regimen than the 600 mg every 12 h (q12h), especially in patients aged between 2 and 12 years since patients at this age group usually have faster clearance of medications. Dosing in pediatric cystic fibrosis patients should be evaluated due to the frequency of hospitalization and drug-resistant pathogens and the differences in the pharmacokinetic profiles with most antibiotics in this population. More studies in term neonates and new studies in preterm neonates are also needed before using this antibiotic in this population.

Because of the increasing concerns of drug-resistant bacteria, more studies involving ceftaroline are expected to assess its possible use for more indications. Currently, ceftaroline is only limited to patients with ABSSSI and CABP. New studies should determine the appropriateness of this antibiotic in other infections typically caused by drug-resistant bacteria. In addition to CABP, ceftaroline could be examined in the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia due to MRSA. The ongoing study of neonatal sepsis [13] could be enhanced with studies of sepsis and bacteremia in all age groups. Ceftaroline may also play a potential role in treating infective endocarditis, septic arthritis, diffuse osteomyelitis and other hematogenous infections. The study measuring the diffusion of ceftaroline into the CSF [14] may yield more studies in the future for the possible treatment of meningitis in the pediatric population.

Lastly, the current literature provides strong evidence on the pharmacokinetic profile and tolerability of ceftaroline in pediatric patients. However, no published or ongoing study has been powered to assess the clinical efficacy of ceftaroline in the respective infections. Ceftaroline is marketed as a treatment for suspected MRSA or PRSP; however, the available pediatric trials either excluded drug-resistant pathogens or included only a small sample of such infections.

6 Conclusion

Ceftaroline fosamil provides an additional therapeutic option for pediatric patients with ABSSSI or CABP. Ceftaroline is well-tolerated in pediatric clinical trials, but current studies are not powered to test equivalence with other agents. Its use should only be limited to cases of suspected drug-resistant pathogens at this time and clinicians should follow current recommended dosing guidelines.

Compliance with Ethical Standards

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