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REVIEW ARTICLE

Ceftaroline Fosamil for Treatment of Pediatric Complicated Skin and Soft Tissue Infections and Community-Acquired Pneumonia

Susanna Esposito[1] · Timothy J. Carrothers[2] · Todd Riccobene[2] · Gregory G. Stone[3] · Michal Kantecki[4]

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Abstract

Community-acquired pneumonia (CAP)/community-acquired bacterial pneumonia (CABP) and complicated skin and soft tissue infection (cSSTI)/acute bacterial skin and skin structure infection (ABSSSI) represent major causes of morbidity and mortality in children. β-Lactams are the cornerstone of antibiotic treatment for many serious bacterial infections in children; however, most of these agents have no activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftaroline fosamil, a β-lactam with broad-spectrum in vitro activity against Gram-positive pathogens (including MRSA and multidrug-resistant *Streptococcus pneumoniae*) and common Gram-negative organisms, is approved in the European Union and the United States for children with CAP/CABP or cSSTI/ABSSSI. Ceftaroline fosamil has completed a pediatric investigation plan including safety, efficacy, and pharmacokinetic evaluations in patients with ages ranging from birth to 17 years. It has demonstrated similar clinical and microbiological efficacy to best available existing treatments in phase III–IV trials in patients aged ≥ 2 months to < 18 years with CABP or ABSSSI, with a safety profile consistent with the cephalosporin class. It is also approved in the European Union for neonates with CAP or cSSTI, and in the US for neonates with ABSSSI. Ceftaroline fosamil dosing for children (including renal function adjustments) is supported by pharmacokinetic/pharmacodynamic modeling and simulations in appropriate age groups, and includes the option of 5- to 60-min intravenous infusions for standard doses, and a high dose for cSSTI patients with MRSA isolates, with a ceftaroline minimum inhibitory concentration of 2–4 mg/L. Considered together, these data suggest ceftaroline fosamil may be beneficial in the management of CAP/CABP and cSSTI/ABSSSI in children.

1 Introduction

Bacterial infection remains a major cause of morbidity and mortality in children [1]. Currently, β-lactams are the cornerstone of antibiotic treatment for many serious bacterial infections in both adults and children; however, the majority of these agents have no activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [2]. Vancomycin is currently recommended as first-line therapy for treatment of MRSA infections in children [3]. However, increasing reports of vancomycin failures in both adult and pediatric patients, and the emergence of reduced-vancomycin-susceptibility phenotypes, together with the requirement for additional safety measures, have led to increased use of newer agents for the treatment of MRSA infections [3–5]. Other antibiotics traditionally used where MRSA is suspected/confirmed are not universally approved for use in children.

The cephalosporin ceftaroline fosamil is a β-lactam with in vitro activity against Gram-positive pathogens, including MRSA and multidrug-resistant *Streptococcus pneumoniae*, and common (non-extended-spectrum β-lactamase-producing) Gram-negative organisms (excluding *Pseudomonas aeruginosa*) [6–8]. Ceftaroline fosamil was initially approved in the European Union and the United States (US) for the treatment of adults with complicated skin and soft tissue infection (cSSTI)/acute bacterial skin and skin structure infection (ABSSSI) and community-acquired pneumonia (CAP)/community-acquired bacterial pneumonia (CABP) (of *S. aureus* infections, only methicillin-susceptible [MSSA] were included) [7, 8]. These approvals were

✉ Susanna Esposito
susannamariaroberta.esposito@unipr.it

1 Pediatric Clinic, Pietro Barilla Children's Hospital, University of Parma, Building 15, Via Gramsci 14, 43126 Parma, Italy

2 AbbVie, Madison, NJ, USA

3 Pfizer, Groton, CT, USA

4 Pfizer, Paris, France

Key Points

Ceftaroline fosamil has broad-spectrum in vitro activity against Gram-positive pathogens (including methicillin-resistant *Staphylococcus aureus* [MRSA] and multidrug-resistant *Streptococcus pneumoniae*) and common Gram-negative organisms, and is approved in Europe and the US for children with complicated skin and soft tissue infection (cSSTI) or community-acquired pneumonia (CAP).

Ceftaroline fosamil pediatric dosing is supported by pharmacokinetic modeling in relevant age groups, and includes the option of 5- to 60-min intravenous infusions for standard doses, and a high dose for cSSTI patients with MRSA isolates, with a ceftaroline minimum inhibitory concentration of 2–4 mg/L.

Ceftaroline fosamil has demonstrated similar clinical and microbiological efficacy to best available existing treatments in children in phase II/III–IV trials, with a safety profile consistent with the cephalosporin class; considered together, the available data indicate that ceftaroline fosamil may have a beneficial role to play in the management of CAP and cSSTI in children.

subsequently extended, based on the completion of additional pediatric studies agreed on as part of the European pediatric investigation plan (PIP) and in line with US *Pediatric Research Equity Act* (PREA) requirements, to include pediatric patients aged ≥ 2 months and, more recently, neonates (with ABSSSI only in the US) [7, 8]. European labeling has recently been further extended to include high-dose recommendations for pediatric patients aged ≥ 2 months to < 18 years with cSSTI [8].

This narrative literature review will explore the epidemiology and current treatment modalities for cSSTI/ABSSSI and CAP/CABP in hospitalized pediatric patients, examine the microbiological activity, clinical pharmacology, and clinical development of ceftaroline fosamil in pediatric patients, and discuss the potential place in therapy for ceftaroline fosamil in the treatment of children with cSSTI/ABSSSI or CAP/CABP.

2 Epidemiology and Current Treatment Patterns of Pediatric CAP/CABP

In European countries, the annual incidence of CAP is approximately 14.4 per 10,000 in children aged over 5 years and 33.8 per 10,000 in those under 5 years of age [9, 10]. Approximately 2 per 1000 children are hospitalized for CAP each year [11]. In the US, the annual incidence of CAP is approximately 15.7 per 10,000 children, with the highest rates among children aged less than 2 years (~ 62.2 per 10,000 children) [12]. CAP represents the leading global cause of mortality in children aged less than 5 years [13, 14], and in 2015, approximately 920,000 children of all ages died due to CAP worldwide [13].

A large multicenter study in the US found that of pediatric patients hospitalized with radiological pneumonia, only 15% had detectable bacteria versus 73% with viral pathogens [12]. The low prevalence of bacterial pneumonia was considered likely to be a reflection of the effectiveness of bacterial conjugate vaccines, as well as relatively insensitive diagnostic methods [12], which remain suboptimal in comparison with the highly sensitive molecular diagnostics developed for viral pathogens [12, 15].

Streptococcus pneumoniae is the most common bacterial cause of CAP in adults [16]. The bacterial etiology of CAP in pediatric patients shows some variation from that of adults and can vary according to age group. Group B *Streptococcus* and Gram-negative enteric bacteria are the most common pathogens in neonates and are typically acquired through vertical transmission from the mother during birth [17]. *S. pneumoniae* is the most common bacterial cause of CAP after the neonatal period [17]. Other important bacterial causes of CAP in children aged less than 5 years include *Haemophilus influenzae*, *Streptococcus pyogenes*, *S. aureus*, and *Moraxella catarrhalis*. In children aged ≥ 5 years, atypical pathogens (*Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*) also contribute to development of CAP [18]. Furthermore, some differences in the etiology and pathophysiology of CAP may exist in pediatric patients aged less than 2 months [19].

There has been an emergence of penicillin-resistant *S. pneumoniae* (PNRP) over the past 3 decades. *S. pneumoniae* strains with reduced penicillin susceptibility also exhibit decreased susceptibility to the majority of other β-lactams [20]. With the success of PCV7, PCV10, and PCV13 vaccination in decreasing invasive pneumococcal infection, there has been a reduction in penicillin resistance in circulating pneumococcal strains [21, 22]. However, treatment challenges still exist in geographic regions where the local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or in the case of inadequate immunization [21]. Guidelines currently advocate higher dosages of β-lactams for the treatment of PNRP where there is no widespread failure of antimicrobial treatment, with dosages similar to those used for the treatment of meningitis in regions with substantial high-level penicillin resistance (minimum inhibitory concentration [MIC] > 8 mg/L) among invasive strains [21, 23].

British Thoracic Society guidelines recommend that all children with a clear diagnosis of pneumonia be treated with antibiotics, as viral and bacterial pneumonia cannot reliably be distinguished from each other [23]. However, guidelines by the Infectious Diseases Society of America suggest antimicrobial therapy may not be routinely required for preschool-aged children with CAP, as viral pathogens are considered to be responsible for the majority of CAP cases in this age group [21]. Antimicrobial therapy for children with CAP is generally initiated empirically [21, 23], and the selected regimen needs to provide activity against the most likely causative pathogens, without excessively broad antimicrobial coverage (to limit antimicrobial resistance development). Therapy should be de-escalated or rationalized whenever possible based on diagnostic culture/susceptibility data. Current treatment options include ceftriaxone, ampicillin, or amoxicillin [21, 23]. Given the treatment challenges of pediatric bacterial CAP, including in cases of documented penicillin- or ceftriaxone-resistant *S. pneumoniae* strains, and polymicrobial infections, there remains a need for alternative potential treatment options, with coverage against the range of potential causative pathogens [24].

3 Epidemiology and Current Treatment Patterns of Pediatric cSSTI/ABSSSI

cSSTI/ABSSSI encompasses a broad range of non-necrotizing infections, including impetigo, erysipelas, cellulitis, major cutaneous abscesses, and surgical site and burn infections, as well as necrotizing infections, such as pyomyositis, necrotizing fasciitis, clostridial myonecrosis, and Fournier's gangrene [25]. The US Food and Drug Administration (FDA) definition of ABSSSI includes a minimum lesion size of approximately 75 cm^2 [26].

In the US, hospital admissions for skin and soft tissue infection increased by 29% between 2000 and 2004, and were the most rapidly increasing cause of hospitalizations between 1997 and 2007 across patients of all ages [27]. A similar trend was observed among pediatric patients between 2000 and 2010 [28]. Hospital admissions for pediatric patients with ABSSSI have similarly become more frequent in recent years [29].

Similar to adults, common etiological bacterial pathogens in cSSTI among all pediatric age groups are *S. pyogenes* and *S. aureus* (including MRSA), and these infections are most often caused by localized opportunistic invasion [30, 31]. Less common causes include other *Streptococcus* spp., *Enterococcus faecalis*, and Gram-negative bacteria.

Treatment guidelines for cSSTI vary depending on the site and severity of the infection [32, 33], but typically involve a combination of surgical debridement, empirical and/or targeted antibiotic therapy, and physiological supportive care [34, 35]. For cSSTI with suspected/confirmed MRSA, treatment options include vancomycin, clindamycin, daptomycin, tigecycline, and linezolid; however, age restrictions limit the approved use of some of these agents in pediatric patients (Supplementary Table S1, see electronic supplementary material [ESM]). Additionally, vancomycin requires therapeutic drug monitoring of trough serum concentrations to avoid potential nephrotoxicity. Furthermore, there have been increasing reports of vancomycin treatment failures in patients with MRSA infections, attributed in part to rising MICs [36, 37], with treatment failure rates of between 30% and 50% reported for children with MRSA bacteremia [4, 5].

Given the limitations of currently available treatments, there is a need for alternative treatment options with activity against key causative cSSTI pathogens, together with a low potential for development of resistance, and a favorable safety profile.

4 Mode of Action and In Vitro Activity of Ceftaroline Fosamil

The phosphono prodrug ceftaroline fosamil is rapidly converted into the active metabolite, ceftaroline, following intravenous (IV) administration [38]. Bacterial resistance mechanisms are predominantly the result of mutations of penicillin-binding proteins (PBPs). As with other β-lactams, the rapid bactericidal effect of ceftaroline is a result of its non-covalent interaction with the transpeptidase domain of key PBPs [39–41]. However, ceftaroline exhibits a greater binding affinity for PBPs in key resistant pathogens, including MRSA (PBP2A) and penicillin-resistant *S. pneumoniae* (PBP2X), in comparison to most other cephalosporins and β-lactams due to its 3′ 1,3-thiazole ring [39, 40, 42]. Ceftaroline is also active against most species of *Enterobacterales* but, like other cephalosporins, has limited activity against isolates producing extended-spectrum β-lactamases from the TEM, SHV, or CTX-M families, serine carbapenemases (such as *Klebsiella pneumoniae* carbapenemase [KPC]), class B metallo-β-lactamases, or class C (AmpC) cephalosporinases [8].

Ceftaroline has demonstrated potent in vitro activity against bacterial isolates causing bloodstream infections in children; Table 1 shows the in vitro activity of several antibiotics against a range of isolates from pediatric patients aged 0–18 years worldwide from the Antimicrobial Testing Leadership And Surveillance (ATLAS) database [43]. Of 8006 *S. aureus* isolates tested, 98.1% were susceptible to ceftaroline ($MIC_{90,}$ 1 mg/L), including 95.9% of 3767 MRSA isolates ($MIC_{90,}$ 1 mg/L), based on both European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) breakpoints. The high PBP-binding affinity of ceftaroline is thought to be responsible for the observed low MICs [8, 41].

The clinical efficacy of ceftaroline has not been established against anaerobic microorganisms, although studies suggest ceftaroline has good in vitro activity against most Gram-positive anaerobes [8, 44]. However, as these pathogens can be treated with other antibiotics, if they are identified as the sole pathogen in a given infection, then ceftaroline would likely be de-escalated to alternative antibiotic therapy.

5 Ceftaroline Fosamil Pediatric Clinical Trials

Ceftaroline fosamil has undergone extensive clinical evaluation in pediatric patients (Table 2), including single-dose pharmacokinetic (PK) studies and multiple-dose safety and efficacy studies in children from birth to less than 18 years of age. It should be noted that safety was the primary endpoint for the clinical studies, and they were not powered for comparative inferential efficacy analysis.

Across three phase II/III–IV trials in patients aged ≥ 2 months to less than 18 years with CABP, complicated CABP, or ABSSSI, ceftaroline fosamil demonstrated generally similar clinical efficacy to standard comparator treatments (Table 2). In the CABP trial, clinical cure rates at test of cure (TOC) were 87.9% (94/107) for ceftaroline fosamil and 88.9% (32/36) for ceftriaxone [45]. Respective clinical cure rates in the complicated CABP trial were 89.7% (26/29) and 100% (9/9) [46]. In the ABSSSI trial, the clinical cure rate at TOC was 94.4% (101/107) for ceftaroline fosamil and 86.5% (45/52) for the comparator (vancomycin or cefazolin, with or without aztreonam) [47].

Patients with MRSA infection were excluded from the CABP trial, due to the inactivity of ceftriaxone against MRSA. There was one patient with MRSA infection included in the complicated CABP trial; this patient was randomized to ceftaroline fosamil, and achieved clinical cure at TOC. In the ABSSSI trial, 94.4% of patients (101/107) with MRSA infection in the ceftaroline fosamil group were clinical cures at TOC, versus 86.5% (45/52) in the comparator group. Not all these investigational trials used the approved pediatric ceftaroline fosamil doses, and they excluded critically ill patients and those with underlying immune dysfunction (Table 2). However, no new safety concerns were identified in any of the trials, and patterns of treatment-emergent adverse events were generally similar to those reported in a pooled analysis of six ceftaroline fosamil phase III trials in adults [48]. A meta-analysis of the three phase II/III–IV pediatric trials concluded that ceftaroline fosamil demonstrated efficacy and safety that was as good as the comparator treatments [49]. However, given the small numbers of children with MRSA infections included in the trials, further studies are warranted to fully assess efficacy in this patient population.

Finally, in a phase II, open-label, non-comparative trial in neonates and very young infants (7–60 days old) with late-onset sepsis, the safety and tolerability of ceftaroline fosamil was consistent with the known ceftaroline fosamil safety profile, with no new safety concerns identified in this patient population [50]. Clinical cure rate at TOC was 50.0% (4/8), with four out of eight patients classified as having 'indeterminate' clinical response, i.e., they were improving clinically to the extent that hospital discharge was possible and were continued on non-study antibiotic therapy to complete a treatment course for documented late-onset sepsis. No patient was classified as a clinical failure.

6 Ceftaroline Fosamil Dosing and Breakpoints

6.1 Pharmacokinetic/Pharmacodynamic Targets

For ceftaroline, in line with other β-lactam antibiotics, the percentage of time that free drug concentrations are above the bacteria MIC during a dosing interval ($fT > MIC$) has been shown to be the PK/pharmacodynamic (PD) index associated with efficacy [51]. In murine thigh and lung infection models, median values of 36% and 44% $fT > MIC$ were associated with 1-log kill of *S. aureus* and *S. pneumoniae,* respectively [51]. Population PK analyses using these non-clinical PK/PD targets were previously used to determine the probability of target attainment (PTA) (results for the 36% target are shown in Table 3), with these analyses supporting the initial pediatric approvals for ceftaroline fosamil [52]. The target of 36% for 1-$\log_{10}$ colony-forming unit (cfu)/mL bacterial reduction for *S. aureus* was derived from a single in vivo study using *S. aureus* isolates with ceftaroline MICs of 0.12–1 mg/L. However, a subsequent analysis of in vitro and in vivo data with *S. aureus* isolates encompassing a greater range of MICs reported PK/PD targets of 27% for stasis, 31% for 1-$\log_{10}$ cfu/mL bacterial reduction, and 35% for 2-$\log_{10}$ reduction [53–55]. Therefore, the PTA analyses using 36% $fT > MIC$ can be considered to be based on a robust PK/PD target.

Since it can be challenging to conduct large-scale efficacy trials in pediatric populations, extrapolation approaches combining observed PK and safety data in children with adult efficacy and safety data and population PK modeling/simulation and PTA analysis are accepted techniques to support antibiotic dose selection and approval in pediatric drug development [56–59]. Using the updated PK/PD targets described above, population PK modeling and simulations have shown that standard ceftaroline fosamil adult and pediatric doses provide high (> 90%) PTA across all age groups against target pathogens at their respective EUCAST and CLSI susceptible MIC breakpoints [53, 60].

Table 1 In vitro activity of various antibacterials against a range of pathogens isolated from pediatric patients (0–18 years of age) worldwide from the ATLAS surveillance database (2004–2018) [43]

Antibacterial/isolate	*n*	Cumulative percentage of isolates at each MIC (mg/L)																% Susceptible	
		0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	EUCAST MIC interpretation	CLSI MIC interpretation
Staphylococcus aureus (overall)																				
Ceftaroline	8006			0.0	0.0	0.3	7.9	54.0	89.4	98.1	99.8	100	100						98.1	98.1
Ceftriaxone	14,003				0.1	0.2	0.3	0.4	0.6	2.5	26.8	58.1	64.3	74.1	81.6	97.0	100		N/A	N/A
Clindamycin	8006				1.0	13.1	83.8	87.1	87.6	87.7	87.9	94.6	100						87.1	87.6
Daptomycin	8006					0.0	1.0	21.5	81.1	99.9	100								99.9	99.9
Gentamicin	5661					0.4	5.7	38.7	53.1	69.6	90.1	90.5	91.1	92.5	94.5	100			69.6	90.5
Levofloxacin	14,911				0.0	3.7	35.0	73.6	80.5	82.2	83.3	92.6	97.4	98.5	99.5	100			0	82.2
Linezolid	14,909								1.2	22.1	95.0	100		100					100	100
Tigecycline	14,911		0.1	0.2	2.2	25.2	76.7	95.5	99.7	99.9	100	100							99.7	99.7
Vancomycin	14,911						0.2	0.9	32.0	93.7	100								100	100
MRSA																				
Ceftaroline	3767			0.0	0.1	0.1	0.2	8.7	78.0	95.9	99.6	100	100						95.9	95.9
Ceftriaxone	5614				0.0	0.0	0.1	0.1	0.1	0.3	0.8	2.8	13.2	36.3	54.6	92.8	100		N/A	N/A
Clindamycin	3767				1.1	12.1	74.7	77.6	78.0	78.2	78.3	89.9	100						77.6	78.0
Daptomycin	3767					0.0	0.6	14.5	77.4	99.9	100								99.9	99.9
Gentamicin	2647					0.3	5.1	39.1	54.6	63.3	83.5	83.9	84.8	86.4	89.7	100			63.3	83.9
Levofloxacin	5827					0.8	20.5	53.3	59.7	61.4	63.0	83.4	94.2	96.6	98.9	100			0	61.4
Linezolid	5825								1.1	25.7	96.8	100	100	100					100	100
Tigecycline	5827		0.1	0.2	1.7	23.6	73.5	94.4	99.6	100	100							0.05	99.6	99.6
Vancomycin	5827						0.2	0.8	25.6	92.3	100								100	100
Streptococcus pneumoniae																				
Ceftaroline	3212	23.0	48.4	59.3	67.0	75.3	91.5	98.2	99.9	100	100	100	100	100	100				98.2	99.9
Ceftriaxone	8835			10.4	51.4	60.7	67.1	72.8	80.1	92.0	97.6	99.0	99.8	99.9	100	100	100		80.1	92.0
Clindamycin	8288		0.3	5.6	29.9	69.5	73.7	74.4	74.7	75.1	86.7	86.8	87.1	87.4	87.7	88.7	100		74.7	74.4
Levofloxacin	8835					0.7	1.6	4.3	38.8	95.6	99.6	99.8	99.8	100	100	100			0	99.6
Linezolid	8835					0.1	0.5	2.3	44.7	93.8	100	100							100	100
Vancomycin	8835		0.0	0.1	0.2	0.5	7.6	63.2	98.5	100									100	100
Penicillin-resistant *S. pneumoniae*																				
Ceftaroline	419		0.2	0.2	3.3	5.7	47.7	86.6	99.3	99.8	99.78	99.8	99.8	99.8	100				86.6	99.3
Ceftriaxone	915			0.1	0.6	0.6	1.1	1.4	4.5	40.9	81.0	91.6	99.0	99.1	99.8	100	100		4.5	40.9
Clindamycin	882			0.5	4.7	18.6	21.8	23.1	23.6	23.8	62.0	62.0	62.1	62.4	62.6	63.8	100		23.6	23.1
Levofloxacin	915						0.3	1.2	24.6	94.1	99.1	99.3	99.3	100					0	99.1

Table 1 (continued)

Antibacterial/isolate	*n*	Cumulative percentage of isolates at each MIC (mg/L)																% Susceptible	
		0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	EUCAST MIC interpretation	CLSI MIC interpretation
Linezolid	915						0.2	2.0	55.5	96.3	100								100	100
Vancomycin	915					0.1	1.6	54.9	97.8	100									100	100
Streptococcus pyogenes																				
Ceftaroline	2733	63.7	97.7	99.5	99.6	99.7	100												N/A	100
Ceftriaxone	3447			33.1	95.7	99.3	99.6	99.7	99.9	100	100								N/A	99.9
Clindamycin	2733		0.2	1.9	39.4	93.4	94.9	95.1	95.2	95.4	100								95.2	95.0
Daptomycin	2485				3.3	36.7	92.0	99.6	99.9	100									100	100
Levofloxacin	3447					0.1	0.6	13.7	73.4	92.8	99.8	100	100	100					0	99.8
Linezolid	3447					0.1	0.2	1.2	25.3	89.3	100								100	100
Tigecycline	3447		2.0	23.7	87.0	99.6	100												100	100
Vancomycin	3447				0.0	0.2	1.3	47.9	98.9	100									100	100
Haemophilus influenzae																				
Ceftaroline	992			68.2	95.9	97.8	98.9	99.5	99.6	99.8	100								95.9	99.6
Ceftriaxone	7672				12.3	95.2	97.4	98.4	99.2	99.6	99.9	100	100	100	100				97.4	99.9
Levofloxacin	7672	0.4	24.0	86.5	96.1	97.3	98.2	98.7	99.4	99.8	99.9	99.9	100	100					97.3	99.9
Enterococcus faecalis																				
Ceftaroline	454						0.7	1.5	8.4	55.7	82.4	87.2	92.1	93.6	97.8	100			N/A	N/A
Ceftriaxone	1946				0.2	0.3	0.3	0.5	0.8	1.8	2.8	3.9	6.6	14.5	25.4	43.3	100		N/A	N/A
Clindamycin	211				0.5	0.5	1.0	1.0	1.4	1.4	2.8	99.1	100						N/A	N/A
Daptomycin	454					0.7	0.7	1.1	13.4	50.2	87.2	100							N/A	87.2
Gentamicin	211									0.5	1.4	3.3	36.5	65.4	99.1	100			N/A	N/A
Levofloxacin	2398					0.2	0.4	1.8	22.1	78.1	86.0	86.8	89.2	92.3	95.8	100			N/A	86.0
Linezolid	2398						0.0	0.0	3.4	40.5	99.8	99.9	100	100					99.9	99.8
Tigecycline	2398		0.2	0.5	6.2	43.9	83.7	99.0	99.8	100	100								99.0	99.0
Vancomycin	2398						0.3	0.8	14.3	67.4	97.2	98.9	99.4	99.5	99.7	100			98.9	98.9
Enterococcus faecium																				
Ceftaroline	232					0.4	1.3	4.7	9.9	17.7	18.5	19.4	21.6	27.6	52.6	100			N/A	N/A
Ceftriaxone	499				0.2	0.6	0.8	0.8	1.2	1.8	3.2	3.8	5.0	6.6	8.8	14.2	100		N/A	N/A
Clindamycin	78				1.3	6.4	20.5	25.6	25.6	28.2	30.8	100							N/A	N/A
Daptomycin	232								0.4	6.9	37.5	97.4	100						N/A	37.5
Gentamicin	78										6.4	30.8	42.3	52.6	100				N/A	N/A
Levofloxacin	731							0.8	3.3	9.4	25.4	30.1	39.1	57.6	63.2	100			N/A	25.4

Table 1 (continued)

Antibacterial/isolate	*n*	Cumulative percentage of isolates at each MIC (mg/L)															% Susceptible	
		0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	EUCAST MIC interpretation	CLSI MIC interpretation
Linezolid	731							0.3	2.5	33.8	98.5	99.3	99.5	100					99.3	98.5
Tigecycline	731		0.3	1.8	28.2	68.3	91.1	99.2	99.7	100									99.2	99.2
Vancomycin	731						0.6	4.1	34.8	68.0	72.9	75.4	77.0	77.7	80.4	100			75.4	75.4

ATLAS Antimicrobial Testing Leadership And Surveillance, *CLSI* Clinical and Laboratory Standards Institute, *EUCAST* European Committee on Antimicrobial Susceptibility Testing, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *N/A* not applicable (as EUCAST/CLSI breakpoints currently not established)

Comparative population PK modeling and PTA analyses based on adult PK data have shown that ceftaroline fosamil achieves superior PK target attainment and PTA against *S. aureus* (at their respective susceptible MIC breakpoints) compared to vancomycin, daptomycin, linezolid, and ceftriaxone in patients with cSSTI [61] and versus ceftriaxone and levofloxacin against *S. aureus*, *S. pneumoniae* and *H. influenzae* in patients with CAP, even for higher than recommended doses for some of these agents [62]. Given that for acute bacterial infections, the pathogens, disease processes, and drug responses are largely the same in adults and pediatric populations, it is reasonable to expect that the above findings would also be applicable to pediatric patients [59, 63, 64].

6.2 Pediatric Dosing

The addition of pediatric dosing recommendations in the European and US labels was based on completion of the PIP and fulfillment of PREA requirements, which included clinical trials in relevant pediatric indications and population PK analyses [60, 65]. In the case of the European label, the pediatric population PK analyses used the PK/PD targets described by Das et al. [53], with these analyses demonstrating drug exposures and PTA in pediatric patients equivalent to adults with normal renal function receiving standard and high ceftaroline fosamil doses.

Owing to various divergences in the respective regulatory review processes, there are several noteworthy differences between the approved European and US pediatric ceftaroline fosamil dosing regimens (Supplementary Table S2, see ESM).

The European label includes standard dose recommendations for neonates with CAP or cSSTI (with dosing at 6 mg/kg every 8 h by 60-min infusion). However, FDA guidance states that, owing to differences in the etiology and pathophysiology of CABP in pediatric patients aged less than 2 months, efficacy findings from adult and pediatric patients more than 2 months of age cannot be extrapolated to infants less than 2 months of age [19]. Therefore, in the US, only neonates with ABSSSI are included in the US label (6 mg/kg every 8 h by 30- to 60-min infusion). Furthermore, while the neonatal age range in the European label is birth to less than 2 months, in the US label, only patients with a gestational age of 34 weeks and older and a postnatal age of 12 days and older are included, based on the age of the patients enrolled in the pediatric clinical studies.

While the majority of *S. aureus* clinical isolates have a ceftaroline MIC of $\leq$ 1 mg/L, surveillance studies have identified rare MRSA isolates with MICs of 2 or 4 mg/L in various regions [53]. In Europe, adult and pediatric high-dose regimens with longer 2-h IV infusions are approved for patients age $\geq$ 2 months with cSSTI caused by rare *S.*

Table 2 Overview of ceftaroline fosamil pediatric clinical trials

Clinicaltrials.gov identifier and study title	Patients		Ceftaroline fosamil dose regimen(s)	Comparator dose regimen(s)	Study objectives/key outcomes
	Key inclusion/exclusion criteria	Age ranges (*n*)			
NCT00633126 Pharmacokinetics of a single dose of ceftaroline in subjects 12–17 years of age receiving antibiotic therapy [52, 93]	Included: Hospitalized patients receiving antibiotic therapy for treatment of a suspected infection of any type Excluded: Epilepsy or seizure disorder Critically ill or unstable patients	12 to < 18 years ($n = 8$)	8 mg/kg (maximum 600 mg), 1-h infusion (single dose)	N/A	*PK profile* Mean (SD) ceftaroline C_{max}: 15,276 (5997) ng/mL *Safety* Occurrence of ≥ 1 (non-serious) TEAE: 5/9 (55.6%) Serious TEAEs: 1/9 (11.1%)
NCT01298843 Pharmacokinetics of a single dose of ceftaroline fosamil in children aged birth to younger than 12 years with suspected or confirmed infection [52]	Included: Hospitalized patients receiving antibiotic therapy for treatment of a suspected infection of any type Excluded: Epilepsy or seizure disorder Moderate or severe renal impairment Aspartate aminotransferase, alanine aminotransferase, or total bilirubin level > 3 times upper limit of normal Receipt of a blood transfusion during the 24-h period before enrolment	6 to < 12 years ($n = 10$) 2 to < 6 years ($n = 8$) 28 days to < 2 years ($n = 12$) Full-term neonates < 28 days ($n = 12$) Preterm neonates (gestational age 32–37 weeks) age < 28 days ($n = 11$)	10 mg/kg (maximum 600 mg), 1-h infusion 15 mg/kg, 1.5-h infusion 8 mg/kg, 1-h infusion 12 mg/kg, 1-h infusion 8 mg/kg, 1-h infusion 8 mg/kg, 1-h infusion (single doses)	N/A	*PK profile*[a] *Safety*[a]
NCT01400867 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 [47]	Included: Presence of ABSSSI warranting initial hospitalization Presence of ABSSSI with measurable margins of erythema, including deeper and/or extensive soft tissue involvement, or required significant therapeutic surgical intervention Excluded: Uncomplicated skin and soft tissue infections History of seizures, excluding well-documented febrile seizure of childhood Clinical signs or suspicion of meningitis	12 to < 18 years ($n = 23$) 6 to < 12 years ($n = 36$) 2 to < 6 years ($n = 23$) 2 months to < 2 years ($n = 25$)	6 months to < 18 years: 12 mg/kg (maximum 400 mg) q8h, 1-h infusion 2 months to < 6 months: 8 mg/kg q8h, 1-h infusion	Vancomycin 15 mg/kg q6h, ≥ 1-h infusion (or maximum 10 mg/min, whichever was longer) Or Cefazolin 75 mg/kg/day q8h, 1-h infusion Optional in conjunction with either vancomycin or cefazolin: aztreonam 30 mg/kg q8h, 1-h infusion	*Safety (safety population)* Occurrence of ≥ 1 TEAE: Ceftaroline fosamil: 51/106 (48.1%) Comparator: 23/53 (43.4%) Most frequent TEAEs in ceftaroline fosamil group: diarrhea (8/106 [7.5%]) and rash (8/106 [7.5%]) *Efficacy (MITT population)* Clinical cure rate at TOC: Ceftaroline fosamil: 101/107 (94.4%) Comparator: 45/52 (86.5%) Treatment difference (95% CI): 7.9% (−1.2 to 20.2)
NCT01530763 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 [45]	Included: Presence of CABP requiring hospitalization and IV antibacterial therapy Excluded: Confirmed or suspected infection with a known ceftriaxone-resistant pathogen (e.g., MRSA or *Pseudomonas aeruginosa*) ICU admission during the study Non-infectious causes of pulmonary infiltrates	12 to < 18 years ($n = 7$) 6 to < 12 years ($n = 19$) 2 to < 6 years ($n = 58$) 2 months to < 2 years ($n = 23$)	6 months to < 18 years: 12 mg/kg (maximum 400 mg) q8h, 1-h infusion 2 months to < 6 months: 8 mg/kg q8h, 1-h infusion	Ceftriaxone 75 mg/kg/day q12h, 30 (±10)-min infusion (maximum 4 g/day)	*Safety (safety population)* Occurrence of ≥ 1 TEAE: Ceftaroline fosamil: 55/121 (45.5%) Comparator: 18/39 (46.2%) Most frequent TEAE in ceftaroline fosamil group: diarrhea (10/121 [8.3%]) *Efficacy (MITT population)* Clinical cure rate at TOC: Ceftaroline fosamil: 94/107 (87.9%) Comparator: 32/36 (88.9%)

Table 2 (continued)

Clinicaltrials.gov identifier and study title	Patients		Ceftaroline fosamil dose regimen(s)	Comparator dose regimen(s)	Study objectives/key outcomes
	Key inclusion/exclusion criteria	Age ranges (*n*)			
NCT01669980 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 [46]	Included: Presence of CABP warranting 3 days of initial hospitalization Confirmed presence of indicators of complicated CABP Excluded: Confirmed or suspected respiratory tract infection attributable to sources other than CABP Non-infectious causes of pulmonary infiltrates	12 to < 18 years ($n = 4$) 6 to < 12 years ($n = 7$) 2 to < 6 years ($n = 12$) 2 months to < 2 years ($n = 6$)	6 months to < 18 years: 15 mg/kg (maximum 600 mg) q8h, 2-h infusion 2 months to < 6 months: 10 mg/kg q8h, 2-h infusion	Ceftriaxone 75 mg/kg/day q12h, 30 (±10)-min infusion (maximum 4 g/day)	*Safety (safety population)* Occurrence of ≥ 1 TEAE: Ceftaroline fosamil: 12/30 (40.0%) Comparator: 8/10 (80.0%) Most frequent TEAE in ceftaroline fosamil group: anemia (3/30 [10.0%]) and pruritis (3/30 [10.0%]) *Efficacy (MITT population)* Clinical cure rate at TOC: Ceftaroline fosamil: 26/29 (89.7%) Comparator: 9/9 (100%) Treatment difference (95% CI): − 10.3% (− 26.7 to 21.0)
NCT02424734 Safety, tolerability and efficacy of ceftaroline in neonates and young infants with late-onset sepsis [50]	Included: Diagnosis of sepsis within 36 h before enrolment Patients meeting at least 1 of the following laboratory criteria: white blood cell count ≤ 4000 × 109/L OR ≥ 20,000 × 109/L; immature to total neutrophil ratio > 0.2; platelet count ≤ 100,000 × 109/L; C-reactive protein > 15 mg/L OR procalcitonin ≥ 2 ng/mL; hyperglycemia OR hypoglycemia; metabolic acidosis Excluded: Refractory septic shock within 24 h before enrolment that does not resolve after 60 min of vasopressor therapy Moderate or severe renal impairment Evidence of progressively fatal underlying disease, or life expectancy of ≤ 60 days Documented history of seizure Requiring or currently taking antiretroviral therapy for HIV or a child from an HIV-positive mother Proven or suspected central nervous system infection Any condition (e.g., cystic fibrosis, urea cycle disorders), antepartum/peripartum factors, or procedures that would, in the opinion of the investigator, make the patient unsuitable for the study, place a patient at risk, or compromise the quality of data	28 to < 60 days ($n = 4$) GA ≥ 37 weeks; 7 to ≤ 28 days ($n = 5$) GA ≥ 34 to < 37 weeks; 7 to ≤ 28 days ($n = 2$)	6 mg/kg q8h, 1-h infusion[b]	N/A	*Safety (safety population)* Occurrence of ≥ 1 TEAE: 5/11 (45.5%) Most frequent TEAE: diarrhea (2/11 [18.2%]) *Efficacy (MITT population)* Clinical cure rate at TOC: 4/8 (50.0%)[c]

ABSSSI acute bacterial skin and skin structure infection, *CABP* community-acquired bacterial pneumonia, *CI* confidence interval, C_{max} maximum plasma concentration, *GA* gestational age, *HIV* human immunodeficiency virus, *ICU* intensive care unit, *IV* intravenous, *MITT* modified intent-to-treat, *MRSA* methicillin-resistant *Staphylococcus aureus*, *N/A* not applicable, *PK* pharmacokinetic(s), *qxh* every *x* h, *TEAE* treatment-emergent adverse event, *TOC* test of cure

[a]No outcomes data available

[b]The initial planned ceftaroline fosamil dosage was 4 mg/kg q8h. However, the protocol was amended to increase the dosage to 6 mg/kg q8h after additional PK data became available. Of the 11 enrolled patients, three (27.3%) received 4 mg/kg ceftaroline fosamil, with the remaining eight (72.7%) receiving 6 mg/kg, subsequent to protocol amendment

[c]All remaining patients were classified as having 'indeterminate' clinical response; they were improving clinically to the extent that hospital discharge was possible and were continued on non-study antibiotic therapy to complete a treatment course for documented late-onset sepsis. No patient was classified as a clinical failure

aureus isolates with ceftaroline fosamil MICs of 2–4 mg/L [8], although ceftaroline fosamil standard dose regimens are appropriate for most patients. In contrast to some countries in Europe and other parts of the world, the MIC_{90} for ceftaroline fosamil against MRSA has remained consistently at 1 mg/L in the US since the initial approval for adults in 2010; as such, no high-dose recommendations are currently included in the US label [7]. In addition, the European label, but not the US label, includes recommended ceftaroline fosamil dose adjustments for pediatric patients with impaired renal function (estimated creatinine clearance [CrCL] ≤ 50 mL/min) [7, 8].

Both EUCAST and CLSI have defined the susceptible MIC breakpoint for standard doses of ceftaroline fosamil against *S. aureus* as ≤ 1 mg/L [66, 67]. Resistance is defined by EUCAST as MIC > 1 mg/L for standard doses and > 2 mg/L for high-dose regimens. Following recently updated CLSI breakpoint definitions, *S. aureus* isolates with ceftaroline MICs of 2–4 mg/L fall into the susceptible dose-dependent category, with resistance defined as MIC ≥ 8 mg/L [67]. EUCAST and CLSI susceptible MIC breakpoints for ceftaroline fosamil against *S. pneumoniae* are 0.25 mg/L and 0.5 mg/L, respectively [66, 67].

6.3 Ceftaroline Fosamil 5-min IV Infusions

A population PK model was used to predict ceftaroline exposure metrics and conduct PTA simulations following ceftaroline fosamil IV infusion durations of 5 or 60 min for patients across a range of age and renal function groups [52, 60]. Ceftaroline fosamil standard doses (Supplementary Table S2, see ESM) administered by 5-min and 60-min IV infusions achieved similar PTA (≥ 99%) against *S. aureus* and *S. pneumoniae* at their respective PK/PD targets at EUCAST/CLSI MIC susceptibility breakpoints in all simulated age groups [60]. These analyses supported the inclusion in European and US labeling of variable infusion times of 5–60 min for standard ceftaroline fosamil doses in adults and children aged ≥ 2 months [7, 8].

6.4 Dosage Adjustments for Renal Impairment

Population PK analyses were used to estimate ceftaroline exposures and PK/PD target attainment for pediatric patients with various degrees of renal impairment (none, mild, moderate, and severe) in support of the inclusion of pediatric patients aged ≥ 2 years in the European label [68]. The approved ceftaroline fosamil dosage regimens in children aged 2–12 years and less than 33 kg (8 mg/kg every 8 h for moderate renal impairment and 6 mg/kg for severe impairment) achieved *f*T > MIC values at least equivalent to, or higher than, adults with normal renal function receiving standard-dose ceftaroline fosamil 600 mg every 12 h. Predicted exposures (maximum plasma concentration [C_{max}] and area under the curve [AUC]) in pediatric patients with moderate or severe renal impairment were similar to those in children with normal renal function or mild renal impairment receiving the respective dose regimens for normal renal function. Exposure metrics did not exceed those in adults receiving high-dose ceftaroline fosamil 600 mg every 8 h. For adolescents aged 12–18 years and greater than 33 kg, the adult-equivalent regimens (400 mg and 300 mg every 12 h, for moderate and severe renal impairment, respectively) were approved based on simulated exposures and *f*T > MIC values.

In the US, no ceftaroline fosamil dosage recommendations are currently available for pediatric patients of any age with moderate or severe renal impairment or end-stage renal disease (CrCL ≤ 50 mL/min) [7]. In Europe, there are currently no approved ceftaroline fosamil dosage recommendations for patients aged less than 2 years with moderate or severe renal impairment or end-stage renal disease [8]. Additional studies in pediatric patients with renal disease are therefore warranted.

6.5 High-Dose Efficacy/Safety Extrapolation

Ceftaroline fosamil high-dose recommendations for pediatric patients aged 2 months to less than 18 years were recently added to European labeling, for rare cases of cSSTI where *S. aureus* with ceftaroline MICs of 2–4 mg/L are suspected/confirmed (Table 2). These dose recommendations were based on additional population PK modeling and exposure and PTA simulations, and exposure-matching to adults and other pediatric indications for extrapolation of efficacy and safety [65]. A combined population PK model for ceftaroline fosamil and ceftaroline, which included data from 1248 participants (pediatric, $n = 304$; adult, $n = 944$), was used in the place of a previously planned clinical trial to assess the efficacy and safety of high-dose ceftaroline fosamil regimens in pediatric patients with cSSTI. For extrapolation of efficacy, the approved pediatric high-dose regimens (including adjustments for moderate or severe renal impairment in patients ≥ 2 years old) achieved similar exposures and PTA to ceftaroline fosamil 600 mg every 8 h, 2-h IV infusions, in adult cSSTI patients with normal renal function in a phase III adult high-dose trial (COVERS), and these doses can therefore be expected to exhibit comparable efficacy to the adult high-dose regimens [65, 69]. For extrapolation of safety, PK exposure predictions for simulated pediatric patients with cSSTI receiving high-dose regimens were compared with observed age-matched data from two clinical trials of pediatric patients with CABP and ABSSSI, and with data from the adult high-dose COVERS study [46, 65, 69]. Median predicted ceftaroline maximum steady-state plasma drug concentrations ($C_{max,ss}$) for the approved pediatric high

doses were below the highest concentrations observed in the pediatric CABP and ABSSSI trials, one of which used high doses of ceftaroline fosamil intended to match the 600 mg every 8 h adult regimen [46, 65]. As there were no adverse events associated with these exposures, safety of the approved ceftaroline fosamil pediatric high-dose regimens can be expected to be in line with observed data from the pediatric clinical trials [65].

7 Future Perspectives

Currently, there are no prospective clinical trial data on ceftaroline fosamil for the treatment of MRSA CAP, as such patients were excluded from the pivotal adult trials [70, 71]. In vitro and non-clinical data, including lung tissue (epithelial lining fluid) penetration data, together with observational and retrospective real-world studies, including the CAPTURE multicenter registry study, suggest that ceftaroline fosamil may have a potential role in the treatment of MRSA CAP [72–77]; however, additional, studies are warranted to fully assess efficacy in this patient population. Further real-world evidence/observational studies of ceftaroline fosamil, including for treatment of MRSA bacteremia, are currently ongoing.

To date, the clinical utility of ceftaroline fosamil in the treatment of central nervous system (CNS) infections has been limited due to a lack of documentation of human cerebrospinal fluid (CSF) penetration and associated questions surrounding optimal dosing, and the severity of illness in this patient population. However, the spectrum and potency of ceftaroline fosamil and its likely CSF penetration into inflamed meninges [78, 79], together with a number of case reports and small case series describing its successful use in patients with CNS infections, including MRSA meningitis [80–84], suggest that it may have the potential to be effective in this context. Additionally, currently, there are limited data on the use of ceftaroline fosamil in children with chronic medical conditions, such as cystic fibrosis. *S. aureus* is the most commonly isolated organism in the early course of cystic fibrosis, while in the later stages of disease, a more mixed flora including *P. aeruginosa,* other Gram-negative pathogens, and *S. aureus* (including MRSA) is commonly encountered [85]. Although ceftaroline fosamil does not have documented activity against *P. aeruginosa*, a small number of clinical and PK studies suggest it may represent an effective treatment option in pediatric patients with cystic fibrosis [86–89]. However, there is some evidence of altered PK in patients with cystic fibrosis [87–89], and further studies are needed to guide optimal ceftaroline fosamil dosing in these patients. PK studies in children with CNS infections and chronic conditions, including cystic fibrosis, are ongoing [90–92].

Table 3 Median (90% prediction interval) probability of target attainment by age and MIC for ceftaroline fosamil standard doses based on simulations for pediatric patients from birth to < 18 years old with normal renal function, using a target of 36% *ft* > MIC [52]

MIC (mg/L)	Age range, ceftaroline fosamil dose[a]														
	1 to < 2 months 6 mg/kg q8h	0 to < 1 months 6 mg/kg q8h	GA 38 to < 40 weeks 6 mg/kg q8h	GA 36 to < 38 weeks 6 mg/kg q8h	GA 34 to < 36 weeks 6 mg/kg q8h	GA 32 to < 34 weeks 6 mg/kg q8h	GA 30 to < 32 weeks 6 mg/kg q8h	12 to < 18 years 600 mg q12h	12 to < 18 years 12 mg/ kg q8h	6 to < 12 years 12 mg/kg q8h	2 to < 6 years 12 mg/ kg q8h	18 to < 24 months 8 mg/kg q8h	12 to < 18 months 8 mg/kg q8h	6 to < 12 months 8 mg/kg q8hg	2 to < 6 months 8 mg/kg q8h	Adults 600 mg q12h
0.125	100	100	100	100		100	100	100	100		100	100	100	100	100	100	
0.25	100	100	100	100		100	100	100	100		100	100	100	100	100	100	
0.5	100	100	100	100		100	100	100	100		100	100	100	100	100	100	
1	100	100	100	100		100	100	99.8	100		100	100	100	100	100	100	99.7
2	98.3	99.0	99.7	99.3	99.0	98.2	96.3	90.1	97.0		99.4	98.2	94.0	95.9	98.5	99.8	81.0
4	37.8	44.7	54.2	47.5	40.3	33.0	26.0	29.5	44.7		71.6	56.8	28.3	36.0	48.4	68.5	17.0
8	0.00	0.333	0.667	0.333	0.333	0.00	0.00	0.750	1.33		5.00	2.25	0.167	0.250	0.833	2.75	0.00

Adapted with permission from Riccobene et al. [52]

GA gestational age, *MIC* minimum inhibitory concentration, *IV* intravenous, *qxh* every *x* h

[a]All doses administered as 1-h IV infusions

8 Conclusions

CAP/CABP and cSSTI/ABSSSI in pediatric patients each continue to represent a significant burden on healthcare systems and are associated with excess morbidity and mortality. Ceftaroline, a β-lactam with broad-spectrum in vitro activity against Gram-positive pathogens (including MRSA and multidrug-resistant *S. pneumoniae*) and common Gram-negative organisms, is approved in Europe for children of all ages with cSSTI or CAP, and in the US for patients with ABSSSI of gestational age ≥ 34 weeks and postnatal age ≥ 12 days, and for patients with CABP ≥ 2 months old.

Ceftaroline fosamil offers several potential advantages over conventional antimicrobial therapies for moderate-to-severe CAP/CABP and cSSTI/ABSSSI in hospitalized pediatric patients, including excellent in vitro coverage against target pathogens, including *S. aureus*, *S. pneumoniae*, β-hemolytic streptococci, and *H. influenzae*, with rapid bactericidal activity; although, as with all antibiotics, there remains a need for ongoing surveillance of resistance to monitor changes in susceptibility patterns, and ceftaroline fosamil should be used in accordance with the principles of antimicrobial stewardship. However, the relatively low potential for development of resistance and favorable safety profile are positive attributes of ceftaroline in this respect. Additionally, there is a lack of activity against *Pseudomonas* and *Acinetobacter* species, which, while not providing a guarantee of absence of selection of resistant pathogens, is a generally positive characteristic in respect to antimicrobial stewardship [41]. Ceftaroline fosamil also provides dosing optimized for high PK/PD target attainment, with the option of flexible 5- to 60-min variable infusion durations for standard doses. There is extensive adult and pediatric clinical trial experience with ceftaroline fosamil, including safety and PK/PD evaluations of high-dose regimens for rare high-MIC pathogens. Additionally, of note, following completion of the PIP, the approved pediatric indications and recommended dosages of ceftaroline fosamil are based on adequate pediatric studies, with dosing recommendations supported by PK/PD modeling and simulations in appropriate age groups.

In summary, the currently available data suggest a role for ceftaroline fosamil in the management of CAP/CABP and cSSTI/ABSSSI in children. Data from ongoing and future observation and real-world studies will allow continued assessment of the effectiveness and safety of ceftaroline fosamil in pediatric patients.

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Declarations

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Conflict of interest Susanna Esposito has received honoraria from Pfizer for speaker presentations in international meetings. Gregory G. Stone and Michal Kantecki are employees of and shareholders in Pfizer. Todd Riccobene is an employee and stockholder of AbbVie (following its acquisition of Allergan). Timothy J. Carrothers is a former employee of AbbVie (following its acquisition of Allergan).

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References

1. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. Pediatr Crit Care Med. 2013;14:686–93.
2. Shang W, Rao Y, Zheng Y, Yang Y, Hu Q, Hu Z, et al. Beta-lactam antibiotics enhance the pathogenicity of methicillin-resistant *Staphylococcus aureus* via SarA-controlled lipoprotein-like cluster expression. MBio. 2019;10:e00880-19.
3. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, 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. Clin Infect Dis. 2011;52:e18-55.
4. Hahn A, Frenck RW Jr, Allen-Staat M, Zou Y, Vinks AA. Evaluation of target attainment of vancomycin area under the curve in children with methicillin-resistant *Staphylococcus aureus* Bacteremia. Ther Drug Monit. 2015;37:619–25.
5. Welsh KJ, Abbott AN, Lewis EM, Gardiner JM, Kruzel MC, Lewis CT, et al. Clinical characteristics, outcomes, and microbiologic features associated with methicillin-resistant *Staphylococcus aureus* bacteremia in pediatric patients treated with vancomycin. J Clin Microbiol. 2010;48:894–9.

6. Pfaller MA, Mendes RE, Flamm RK, Jones RN, Sader HS. Ceftaroline activity against multidrug-resistant *Streptococcus pneumoniae* from U.S. medical centers (2014) and molecular characterization of a single ceftaroline nonsusceptible isolate. Microb Drug Resist. 2017;23:571–9.
7. Allergan. TEFLARO™ (ceftaroline fosamil) injection for intravenous (IV) use. 2020. https://www.allergan.com/assets/pdf/teflaro_pi. Accessed 28 Apr 2021
8. Pfizer. Zinforo 600 mg powder for concentrate for solution for infusion: summary of product characteristics. 2020. https://www.ema.europa.eu/en/documents/product-information/zinforo-epar-product-information_en.pdf. Accessed 28 Apr 2021
9. Senstad AC, Surén P, Brauteset L, Eriksson JR, Høiby EA, Wathne KO. Community-acquired pneumonia (CAP) in children in Oslo, Norway. Acta Paediatr. 2009;98:332–6.
10. Clark JE, Hammal D, Hampton F, Spencer D, Parker L. Epidemiology of community-acquired pneumonia in children seen in hospital. Epidemiol Infect. 2007;135:262–9.
11. Messinger AI, Kupfer O, Hurst A, Parker S. Management of pediatric community-acquired bacterial pneumonia. Pediatr Rev. 2017;38:394–409.
12. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372:835–45.
13. Haq IJ, Battersby AC, Eastham K, McKean M. Community acquired pneumonia in children. BMJ. 2017;356: j686.
14. Rodrigues CMC, Groves H. Community-acquired pneumonia in children: the challenges of microbiological diagnosis. J Clin Microbiol. 2018;56:e01318-17.
15. Katz SE, Williams DJ. Pediatric community-acquired pneumonia in the United States: changing epidemiology, diagnostic and therapeutic challenges, and areas for future research. Infect Dis Clin N Am. 2018;32:47–63.
16. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415–27.
17. Ostapchuk M, Roberts DM, Haddy R. Community-acquired pneumonia in infants and children. Am Fam Physician. 2004;70:899–908.
18. Leung AKC, Wong AHC, Hon KL. Community-acquired pneumonia in children. Recent Pat Inflamm Allergy Drug Discov. 2018;12:136–44.
19. US Food and Drug Administration. Multidisciplinary review and evaluation of efficacy supplemental NDA 200327 S-22 Teflaro—ceftaroline fosamil. 2018. https://www.fda.gov/media/132146/download. Accessed 26 May 2020
20. Oliphant CM, Eroschenko K. Antibiotic resistance, part 1: Gram-positive pathogens. J Nurse Pract. 2015;11:70–8.
21. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011;53:e25-76.
22. Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. Proc Natl Acad Sci U S A. 2018;115:12896–901.
23. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax. 2011;66(Suppl 2):ii1-23.
24. Yim J, Molloy LM, Newland JG. Use of ceftaroline fosamil in children: review of current knowledge and its application. Infect Dis Ther. 2017;6:57–67.
25. Esposito S, Bassetti M, Concia E, De Simone G, De Rosa FG, Grossi P, et al. Diagnosis and management of skin and soft-tissue infections (SSTI). A literature review and consensus statement: an update. J Chemother. 2017;29:197–214.
26. US Food Drug and Administration. Guidance for industry acute bacterial skin and skin structure infections: developing drugs for treatment. 2013. https://www.fda.gov/media/71052/download. Accessed 5 May 2020
27. Miller LG, Eisenberg DF, Liu H, Chang CL, Wang Y, Luthra R, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005–2010. BMC Infect Dis. 2015;15:362.
28. Mistry RD, Weisz K, Halden SF, Alpern ER. Emergency management of pediatric skin and soft tissue infections in the community-associated methicillin-resistant *Staphylococcus aureus* era. Acad Emerg Med. 2010;17:187–93.
29. Moore SJ, O'Leary ST, Caldwell B, Knepper BC, Pawlowski SW, Burman WJ, et al. Clinical characteristics and antibiotic utilization in pediatric patients hospitalized with acute bacterial skin and skin structure infection. Pediatr Infect Dis J. 2014;33:825–8.
30. Lindquist B, Wang NE, Felter RA. Diagnosis and treatment of skin and soft tissue infections. Pediatr Emerg Med Rep. 2015;20:69–79.
31. Scott LJ. Ceftaroline fosamil: a review in complicated skin and soft tissue infections and community-acquired pneumonia. Drugs. 2016;76:1659–74.
32. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e10-52.
33. Galli L, Venturini E, Bassi A, Gattinara GC, Chiappini E, Defilippi C, et al. Common community-acquired bacterial skin and soft-tissue infections in children: an intersociety consensus on impetigo, abscess, and cellulitis treatment. Clin Ther. 2019;41:532-51.e17.
34. Leong HN, Kurup A, Tan MY, Kwa ALH, Liau KH, Wilcox MH. Management of complicated skin and soft tissue infections with a special focus on the role of newer antibiotics. Infect Drug Resist. 2018;11:1959–74.
35. Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother. 2010;65(Suppl 3):iii35-44.
36. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis. 2012;54:755–71.
37. Wilcox M, Al-Obeid S, Gales A, Kozlov R, Martinez-Orozco JA, Rossi F, et al. Reporting elevated vancomycin minimum inhibitory concentration in methicillin-resistant *Staphylococcus aureus*: consensus by an International Working Group. Future Microbiol. 2019;14:345–52.
38. Zhanel GG, Sniezek G, Schweizer F, Zelenitsky S, Lagace-Wiens PR, Rubinstein E, et al. Ceftaroline: a novel broad-spectrum cephalosporin with activity against meticillin-resistant *Staphylococcus aureus*. Drugs. 2009;69:809–31.
39. Ishikawa T, Matsunaga N, Tawada H, Kuroda N, Nakayama Y, Ishibashi Y, et al. TAK-599, a novel *N*-phosphono type prodrug of anti-MRSA cephalosporin T-91825: synthesis, physicochemical and pharmacological properties. Bioorg Med Chem. 2003;11:2427–37.
40. Moisan H, Pruneau M, Malouin F. Binding of ceftaroline to penicillin-binding proteins of *Staphylococcus aureus* and *Streptococcus pneumoniae*. J Antimicrob Chemother. 2010;65:713–6.
41. Laudano JB. Ceftaroline fosamil: a new broad-spectrum cephalosporin. J Antimicrob Chemother. 2011;66 Suppl 3:iii11-8.
42. European Medicines Agency. Zinforo Assessment Report. 2019. https://www.ema.europa.eu/en/documents/variation-report/zinforo-h-c-2252-ii-0041-epar-assessment-report-variation_en.pdf. Accessed 6 May 2020

43. ATLAS. Antibacterials Database. 2020. https://www.atlas-surveillance.com. Accessed 05 May 2021
44. Snydman DR, Jacobus NV, McDermott LA. In vitro activity of ceftaroline against a broad spectrum of recent clinical anaerobic isolates. Antimicrob Agents Chemother. 2011;55:421–5.
45. Cannavino CR, Nemeth A, Korczowski B, Bradley JS, O'Neal T, Jandourek A, et al. A randomized, prospective study of pediatric patients with community-acquired pneumonia treated with ceftaroline versus ceftriaxone. Pediatr Infect Dis J. 2016;35:752–9.
46. Blumer JL, Ghonghadze T, Cannavino C, O'Neal T, Jandourek A, Friedland HD, et al. A multicenter, randomized, observer-blinded, active-controlled study evaluating the safety and effectiveness of ceftaroline compared with ceftriaxone plus vancomycin in pediatric patients with complicated community-acquired bacterial pneumonia. Pediatr Infect Dis J. 2016;35:760–6.
47. Korczowski B, Antadze T, Giorgobiani M, Stryjewski ME, Jandourek A, Smith A, et al. A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety and efficacy of ceftaroline versus comparator in pediatric patients with acute bacterial skin and skin structure infection. Pediatr Infect Dis J. 2016;35:e239–47.
48. Cheng K, Pypstra R, Yan JL, Hammond J. Summary of the safety and tolerability of two treatment regimens of ceftaroline fosamil: 600 mg every 8 h versus 600 mg every 12 h. J Antimicrob Chemother. 2019;74:1086–91.
49. Chen CW, Chang SP, Huang HT, Tang HJ, Lai CC. The efficacy and safety of ceftaroline in the treatment of acute bacterial infection in pediatric patients—a systemic review and meta-analysis of randomized controlled trials. Infect Drug Resist. 2019;12:1303–10.
50. Bradley JS, Stone GG, Chan PLS, Raber SR, Riccobene T, Mas Casullo V, et al. Phase 2 study of the safety, pharmacokinetics and efficacy of ceftaroline fosamil in neonates and very young infants with late-onset sepsis. Pediatr Infect Dis J. 2020;39:411–8.
51. Andes D, Craig WA. Pharmacodynamics of a new cephalosporin, PPI-0903 (TAK-599), active against methicillin-resistant *Staphylococcus aureus* in murine thigh and lung infection models: identification of an *in vivo* pharmacokinetic-pharmacodynamic target. Antimicrob Agents Chemother. 2006;50:1376–83. Erratum in: Antimicrob Agents Chemother. 2014;58:489.
52. Riccobene TA, Khariton T, Knebel W, Das S, Li J, Jandourek A, et al. 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. J Clin Pharmacol. 2017;57:345–55.
53. Das S, Li J, Iaconis J, Zhou D, Stone GG, Yan JL, et al. Ceftaroline fosamil doses and breakpoints for *Staphylococcus aureus* in complicated skin and soft tissue infections. J Antimicrob Chemother. 2019;74:425–31.
54. MacGowan AP, Noel AR, Tomaselli S, Bowker KE. Pharmacodynamics of ceftaroline against *Staphylococcus aureus* studied in an in vitro pharmacokinetic model of infection. Antimicrob Agents Chemother. 2013;57:2451–6.
55. Singh R, Almutairi M, Alm R, Lahiri S, San Martin M, Chen A, et al. Ceftaroline efficacy against high-MIC clinical *Staphylococcus aureus* isolates in an in vitro hollow-fibre infection model. J Antimicrob Chemother. 2017;72:2796–803.
56. US Food and Drug Administration. General clinical pharmacology considerations for pediatric studies for drugs and biological products. 2014. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-and-biological-products. Accessed 06 July 2021
57. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011;128:e1242–9.
58. Mulugeta Y, Barrett JS, Nelson R, Eshete AT, Mushtaq A, Yao L, et al. Exposure matching for extrapolation of efficacy in pediatric drug development. J Clin Pharmacol. 2016;56:1326–34.
59. European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics. 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf. Accessed 28 Feb 2020
60. Riccobene TA, Carrothers TJ, Knebel W, Raber S, Chan PLS. Pharmacokinetic and pharmacodynamic target attainment in adult and pediatric patients following administration of ceftaroline fosamil as a 5-minute infusion. Clin Pharmacol Drug Dev. 2021;10:420–7.
61. Cristinacce A, Wright JG, MacPherson M, Iaconis J, Das S. Comparing probability of target attainment against *Staphylococcus aureus* for ceftaroline fosamil, vancomycin, daptomycin, linezolid, and ceftriaxone in complicated skin and soft tissue infection using pharmacokinetic/pharmacodynamic models. Diagn Microbiol Infect Dis. 2021;99: 115292.
62. Cristinacce A, Wright JG, Stone GG, Hammond J, McFadyen L, Raber S. A retrospective analysis of probability of target attainment in community-acquired pneumonia: Ceftaroline fosamil versus comparators. Infect Dis Ther. 2019;8:185–98.
63. Ollivier C, Thomson A, Manolis E, Blake K, Karlsson KE, Knibbe CAJ, et al. Commentary on the EMA reflection paper on the use of extrapolation in the development of medicines for paediatrics. Br J Clin Pharmacol. 2019;85:659–68.
64. US Food and Drug Administration. Leveraging existing clinical data for extrapolation to pediatric uses of medical devices. 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/leveraging-existing-clinical-data-extrapolation-pediatric-uses-medical-devices. Accessed 28 Feb 2020
65. Chan PLS, McFadyen L, Quaye A, Leister-Tebbe H, Hendrick VM, Hammond J, et al. The use of extrapolation based on modeling and simulation to support high-dose regimens of ceftaroline fosamil in pediatric patients with complicated skin and soft-tissue infections. CPT Pharm Syst Pharmacol. 2021;10:551–63.
66. European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints for bacteria, v 10.0. 2020. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_10.0_Breakpoint_Tables.pdf. Accessed 04 Dec 2020
67. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, 30th edition. CLSI Supplement M100. 2020. http://em100.edaptivedocs.net/GetDoc.aspx?doc=CLSI%20M100%20ED30:2020. Accessed 04 Dec 2020
68. Das S, Riccobene TA, Carrothers TJ, T. K, Knebel W, Melnick D, et al. Ceftaroline fosamil dose adjustments for paediatric patients aged two or more years with moderate and severe renal impairment. In: 27th european congress of clinical microbiology and infectious diseases (ECCMID). Vienna, Austria. 2017. p. P1184.
69. Dryden M, Zhang Y, Wilson D, Iaconis JP, Gonzalez J. A Phase III, randomized, controlled, non-inferiority trial of ceftaroline fosamil 600 mg every 8 h versus vancomycin plus aztreonam in patients with complicated skin and soft tissue infection with systemic inflammatory response or underlying comorbidities. J Antimicrob Chemother. 2016;71:3575–84.
70. File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother. 2011;66(Suppl 3):iii19-32.
71. Low DE, File TM Jr, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. FOCUS 2: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil

versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother. 2011;66(Suppl 3):iii33-44.
72. Karki A, Thurm C, Cervellione K. Experience with ceftaroline for treatment of methicillin-resistant *Staphylococcus aureus* pneumonia in a community hospital. J Community Hosp Intern Med Perspect. 2017;7:300–2.
73. Ramani A, Udeani G, Evans J, Jandourek A, Cole P, Smith A, et al. Contemporary use of ceftaroline fosamil for the treatment of community-acquired bacterial pneumonia: CAPTURE study experience. J Chemother. 2014;26:229–34.
74. Carreno JJ, Lodise TP. Ceftaroline fosamil for the treatment of community-acquired pneumonia: from FOCUS to CAPTURE. Infect Dis Ther. 2014;3:123–32.
75. Biedenbach DJ, Iaconis JP, Sahm DF. Comparative in vitro activities of ceftaroline and ceftriaxone against bacterial pathogens associated with respiratory tract infections: results from the AWARE surveillance study. J Antimicrob Chemother. 2016;71:3459–64.
76. Riccobene TA, Pushkin R, Jandourek A, Knebel W, Khariton T. Penetration of ceftaroline into the epithelial lining fluid of healthy adult subjects. Antimicrob Agents Chemother. 2016;60:5849–57.
77. Welte T, Kantecki M, Stone GG, Hammond J. Ceftaroline fosamil as a potential treatment option for *Staphylococcus aureus* community-acquired pneumonia in adults. Int J Antimicrob Agents. 2019;54:410–22.
78. Croisier-Bertin D, Piroth L, Charles PE, Larribeau A, Biek D, Ge Y, et al. Ceftaroline versus ceftriaxone in a highly penicillin-resistant pneumococcal pneumonia rabbit model using simulated human dosing. Antimicrob Agents Chemother. 2011;55:3557–63.
79. Cottagnoud P, Cottagnoud M, Acosta F, Stucki A. Efficacy of ceftaroline fosamil against penicillin-sensitive and -resistant *Streptococcus pneumoniae* in an experimental rabbit meningitis model. Antimicrob Agents Chemother. 2013;57:4653–5.
80. Sakoulas G, Nonejuie P, Kullar R, Pogliano J, Rybak MJ, Nizet V. Examining the use of ceftaroline in the treatment of *Streptococcus pneumoniae* meningitis with reference to human cathelicidin LL-37. Antimicrob Agents Chemother. 2015;59:2428–31.
81. Kuriakose SS, Rabbat M, Gallagher JC. Ceftaroline CSF concentrations in a patient with ventriculoperitoneal shunt-related meningitis. J Antimicrob Chemother. 2015;70:953–4.
82. Balouch MA, Bajwa RJ, Hassoun A. Successful use of ceftaroline for the treatment of MRSA meningitis secondary to an infectious complication of lumbar spine surgery. J Antimicrob Chemother. 2015;70:624–5.
83. Bucheit J, Collins R, Joshi P. Methicillin-resistant *Staphylococcus aureus* epidural abscess treated with ceftaroline fosamil salvage therapy. Am J Health Syst Pharm. 2014;71:110–3.
84. Cies JJ, Moore WS 2nd, Enache A, Chopra A. Ceftaroline cerebrospinal fluid penetration in the treatment of a ventriculopleural shunt infection: a case report. J Pediatr Pharmacol Ther. 2020;25:336–9.
85. Strausbaugh SD, Davis PB. Cystic fibrosis: a review of epidemiology and pathobiology. Clin Chest Med. 2007;28:279–88.
86. Branstetter J, Searcy H, Benner K, Yarbrough A, Crowder C, Troxler B. Ceftaroline vs vancomycin for the treatment of acute pulmonary exacerbations in pediatric patients with cystic fibrosis. Pediatr Pulmonol. 2020;55:3337–42.
87. Barsky EE, Pereira LM, Sullivan KJ, Wong A, McAdam AJ, Sawicki GS, et al. Ceftaroline pharmacokinetics and pharmacodynamics in patients with cystic fibrosis. J Cyst Fibros. 2018;17:e25–31.
88. Le J, Bradley JS, Hingtgen S, Skochko S, Black N, Jones RN, et al. Pharmacokinetics of single-dose ceftaroline fosamil in children with cystic fibrosis. Pediatr Pulmonol. 2017;52:1424–34.
89. Autry EB, Rybak JM, Leung NR, Gardner BM, Burgess DR, Anstead MI, et al. Pharmacokinetic and pharmacodynamic analyses of ceftaroline in adults with cystic fibrosis. Pharmacotherapy. 2016;36:13–8.
90. ClinicalTrials.gov. Ceftaroline for treatment of hematogenously acquired *Staphylococcus aureus* osteomyelitis in children. ClinicalTrials.gov Identifier: NCT02335905. https://clinicaltrials.gov/ct2/show/NCT02335905?term=ceftaroline&rank=21. Accessed 10 Sep 2020
91. ClinicalTrials.gov. Ceftaroline diffusion into cerebrospinal fluid of children. ClinicalTrials.gov identifier: NCT02600793. https://clinicaltrials.gov/ct2/show/NCT02600793. Accessed 10 Sep 2020.
92. ClinicalTrials.gov. Pharmacokinetic and pharmacodynamic analysis of ceftaroline in children and adolescents with cystic fibrosis. ClinicalTrials.gov Identifier: NCT03771313. https://clinicaltrials.gov/ct2/show/NCT03771313?term=ceftaroline&draw=2&rank=2. Accessed 20 Sep 2020
93. ClinicalTrials.gov. Pharmacokinetics of a single dose of ceftaroline in subjects 12 to 17 years of age receiving antibiotic therapy. ClinicalTrials.gov Identifier: NCT00633126. https://clinicaltrials.gov/ct2/show/NCT00633126. Accessed 16 Feb 2021