Review Article

Ceftaroline—An Anti-MRSA Cephalosporin and Its Implications for Singapore

Hui Hiong Chen, [1]*MPharm*, Pei Yun Hon, [2]*BSc*, Li Yang Hsu, [2]*MBBS, MPH*

Abstract

Introduction: Ceftaroline is a fifth-generation cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) that was recently launched in Singapore. It received approval from the United States (US) Food Drug Administration (FDA) and European Commission for the treatment of adult patients with community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSTI). This study aimed to review current published data and determine its clinical role, particularly in the local setting. Materials and Methods: A literature review on published articles in English on ceftaroline, focusing in particular on clinical trials and other clinical reports. Susceptibility testing was also performed on a limited sample of local MRSA and *Streptococcus pneumoniae* isolates. Results: Ceftaroline has an extensive spectrum of activity, including coverage of MRSA and multidrug-resistant *S. pneumoniae*. However, it has limited activity against non-fermenting Gram-negative bacteria and is susceptible to hydrolysis by extended spectrum beta-lactamases. It is only available for intravenous delivery, with a reconstituted stability of just 6 hours, rendering it unavailable for use for outpatient antibiotic therapy. Clinical trials demonstrate non-inferiority compared to first-line comparators in the treatment of CAP and cSSTI. Published case reports/series suggest a potential greater role in the treatment of MRSA bacteremia and endocarditis. No resistance was found among local archived MRSA and *S. pneumoniae* isolates. Conclusion: We believe ceftaroline will occupy primarily niche roles for culture-directed treatment of various infections—in particular those caused by MRSA—until further clinical trial data become available. A variety of factors render it less useful or appealing for empirical treatment of CAP or healthcare-associated infections.

Ann Acad Med Singapore 2014;43:177-86

Key words: Antimicrobial agent, Bacteremia, Pharmacodynamics, Pharmacokinetics, Vancomycin hetero-resistant *Staphylococcus aureus*

Introduction

Ceftaroline fosamil (TAK-599 or PPI-0903)—the prodrug of the active metabolite, ceftaroline—was launched in Singapore in March 2013 under the tradename Zinforo® by AstraZeneca. It is designated as a member of a new subclass of cephalosporins with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) by the Clinical Laboratory Standards Institute (CLSI) of the USA.[1] Ceftaroline has also been described in the medical literature as a 'fifth-generation' cephalosporin.[2] Ceftaroline was approved by the United States (US) Food and Drug Administration (FDA) in October 2010[3] and the European Commission in August 2012[4] for the treatment of adult patients with community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSTI). The Health Sciences Authority approved it for the same indications in Singapore in November 2012.[5]

This article will provide an overview of ceftaroline, including its mechanism of action, spectrum of activity, pharmacokinetics and pharmacodynamics, clinical efficacy, case reports on its use in other types of infections, as well as its clinical limitations and potential use in the Singapore healthcare setting.

Chemical Structure and Mechanism of Action

The structure of ceftaroline fosamil is shown in Figure 1. As with other beta-lactam antibiotics, ceftaroline's anti-bacterial activity results from the binding of the drug to

[1]Department of Pharmacy, National University Health System, Singapore
[2]Department of Medicine, National University Health System, Singapore
Address for Correspondence: Dr Li Yang Hsu, Department of Medicine, National University Health System, 1E Kent Ridge Road, NUHS Tower Block Level 10, Singapore 119228.
Email: liyang_hsu@yahoo.com

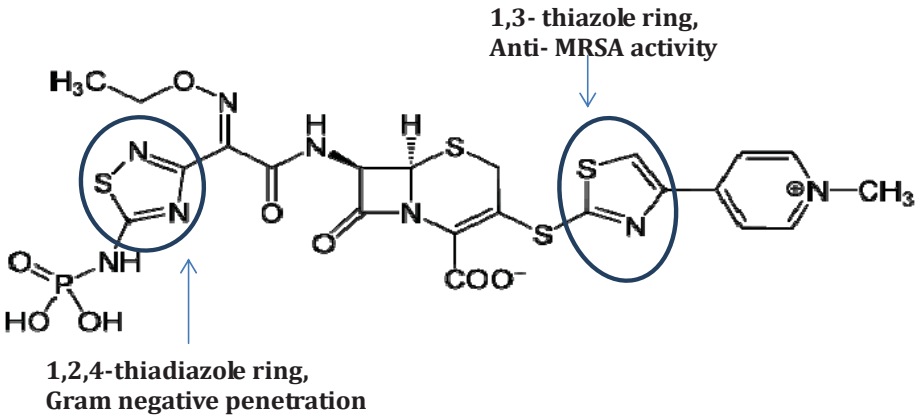

Fig. 1. Chemical structure of ceftaroline fosamil. (Adapted from Wikipedia - https://en.wikipedia.org/wiki/File:Ceftarolinfosamil.svg.)

penicillin-binding proteins (PBPs), thereby interfering with bacterial cell wall synthesis. MRSA is resistant to almost all beta-lactam antibiotics because of the presence of the *mec*A gene encoding a modified PBP 2a with poor binding affinity for these drugs.[6] Ceftaroline binds to PBPs 1-4 and also equally strongly to PBP 2a in MRSA – the latter believed to be due to the addition of a 1,3-thiazole ring at the 3' position of the cephem ring (Fig. 1).[7,8] It is also able to bind to the PBPs that confer beta-lactam resistance in *Streptococcus pneumoniae* (i.e. PBP 2b, PBP 2x, etc.), and thus is also active against multidrug-resistant pneumococci.[8, 9]

The retention of the 1,2,4-thiadiazole ring (Fig. 1) permits penetration past the Gram-negative cell wall, with activity against the majority of Enterobacteriaceae and other Gram-negative bacteria.[10] However, the coverage is variable, as further described below.

Table 1. Spectrum of Activity of Ceftaroline, Including MIC_{90} Results Against Specific Organisms Where Available[11,12]

Organism (number of isolates)	MIC 90s (mcg/mL) of Ceftaroline
Gram positive	
Staphylococcus aureus	
MSSA (348)	0.25
MRSA (92)	1
VISA (20)	1
VRSA (10)	0.5
Coagulase-negative staphylococci	
Methicillin susceptible (201)	0.12
Methicillin resistant (299)	0.5
Enterococcus faecalis	
Vancomycin susceptible (157)	4
Vancomycin resistant (25)	4
Enterococcus faecium (157)	>16
Streptococcus pyogenes	
Erythromycin susceptible (91)	<0.008
Erythromycin resistant (10)	<0.015
Streptococcus agalactiae	
Erythromycin susceptible (59)	0.015
Erythromycin resistant (42)	0.015
Streptococcus pneumoniae	
Penicillin sensitive (202)	0.015
Penicillin intermediate (103)	0.06
Penicillin resistant (296)	0.12

Table 1. Spectrum of Activity of Ceftaroline, Including MIC_{90} Results Against Specific Organisms Where Available[11,12] (Con't)

Organism (number of isolates)	MIC 90s (mcg/mL) of Ceftaroline
Gram negative	
Enterobacteriaceae	
Ceftazidime susceptible (833)	1
Ceftazidime resistant (220)	>16
Citrobacter freundii	
Ceftazidime susceptible (50)	0.25
Ceftazidime resistant (33)	>16
Enterobacter cloacae	
Ceftazidime susceptible (50)	1
Ceftazidime resistant (35)	>16
Escherichia coli	
Ceftazidime Susceptible (345)	0.5
Ceftazidime resistant (63)	>16
Klebsiella pneumoniae	
Ceftazidime susceptible (210)	0.25
Ceftazidime susceptible (66)	>16
Proteus mirabilis (58)	4
Providencia species (27)	>16
Serratia marcescens (59)	16
Acinetobacter species	
Imipenem susceptible (47)	16
Imipenem resistant (16)	>16
Pseudomonas aeruginosa (20)	>32

Spectrum of Activity

The list of organisms against which ceftaroline has demonstrated in vitro activity is shown in Table 1 along with the MIC_{90}'s (the minimum concentration of the drug wherein 90% of the tested isolates were inhibited) where available.[11,12] It is in general active against all *S. aureus* isolates, including those isolates that are non-susceptible to vancomycin, linezolid and/or daptomycin.[10-13] The European Committee on Antimicrobial Susceptibility Testing (EUCAST)[14] and CLSI1 recommended breakpoint for *S. aureus* is currently 1 mcg/mL. It is also active against *Streptococcus pyogenes* and *Streptococcus agalactiae*, with all tested isolates inhibited by concentrations of ≤0.015 μg/mL.[11] All *Streptococcus pneumoniae* isolates, regardless of phenotype, were inhibited at concentration levels below the EUCAST and CLSI recommended breakpoint of 0.25 μg/mL and 0.5 μg/mL respectively.

We had performed ceftaroline susceptibility testing on 40 well-characterised MRSA isolates (Table 2)[15-17] and 40 well-characterised *S. pneumoniae* isolates (Table 3)[18] via both Etest and microbroth dilution. The results mirrored international findings,[10-13] where both organisms were susceptible to ceftaroline despite the presence of resistance to other commonly-used antibiotics. The Etest MIC_{90} for local MRSA and *S. pneumoniae* was 1.0 μg/mL and 0.125 μg/mL respectively, with slightly higher MICs seen for healthcare-associated MRSA clones and penicillin-resistant S. pneumoniae isolates.

Ceftaroline is active against ampicillin-susceptible *Enterococcus faecalis* (even vancomycin-resistant isolates) and ampicillin-susceptible *Enterococcus faecium* in vitro,[10] but there is little clinical experience to support these results at present, and neither CLSI nor EUCAST have issued recommended breakpoints against these organisms.

Ceftaroline has variable activity against many Gram-negative Enterobacteriaceae (Table 1).[10,11] Like the majority of cephalosporins, the drug is susceptible to inactivation by extended-spectrum beta-lactamases and *amp*C beta-lactamases, hence it is potentially inactive against organisms that produce such enzymes.[10] It also has limited activity against non-fermenting Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, with MIC_{90} of >16 μg/mL for such organisms.[10,11]

Ceftaroline possesses anti-anaerobic activity similar to that of amoxicillin-clavulanate against Gram-positive anaerobes and 4- to 8-fold greater activity than that of ceftriaxone.[19] It has limited activity against Gram-negative anaerobes, particularly members of the *Bacteroides fragilis* group, but is active against most beta-lactamase–negative anaerobes, including *Actinomyces spp.*, *Propionibacterium spp.*, *Eubacterium spp.*, *Clostridium perfringens*, *Clostridium ramosum*, and *Clostridium innocuum*.[19]

The drug has no activity against atypical organisms and mycobacteria. In summary, ceftaroline demonstrates potent activity against Gram-positive organisms but only moderate activity against Gram-negative organisms in vitro.

Pharmacokinetics

Ceftaroline fosamil is a prodrug that undergoes rapid dephosphorylation in the bloodstream to the active compound after infusion.[20] The volume of distribution is 28.3 L (0.37 L/kg; range, 0.31 to 0.45 L/kg), representing distribution into the total body water compartment. The drug does not significantly bind to serum proteins (<20% protein-bound), and undergoes further conversion by hydrolysis of its beta-lactam ring to form an inactive, open-ring metabolite (ceftaroline M-1). The average half-life of ceftaroline and ceftaroline M-1 is 2.6 hours and 4.5 hours respectively. The CYP450 system does not appear to be a significant metabolic pathway for ceftaroline, which implies that this drug has a low potential for drug-drug interactions.[20]

Approximately 50% of the dose of ceftaroline is excreted as active drug in the urine. In patients with mild renal impairment (creatinine clearance [CrCl] of 50 to 80 mL/min), the area under the curve (AUC) was 25% higher and the half-life 14% longer. In patients with moderate renal impairment (CrCl 30 to 50 mL/min), the AUC was 50% higher. Because of these characteristics, ceftaroline should be used with caution in patients with moderate to severe renal impairment, and dosing adjustments according to renal function are advised.[8] The dosing recommendation for intravenous dosing is as follows, depending on the CrCl:[20,21]

- >50 mL/min: no adjustment (600 mg every 12 hours).
- 30 to 50 mL/min: 400 mg every 12 hours.
- 15 to 30 mL/min: 300 mg every 12 hours.
- <15 mL/min and patients on dialysis: 200 mg every 12 hours.

Pharmacodynamics

As with other beta-lactams, ceftaroline exhibits time-dependent killing. The amount of time that the serum concentration remains above the MIC represents the main pharmacodynamic predictor of efficacy.

A minimal post-antibiotic effect ranging from 1.9 hours to 7.2 hours for *S. pneumoniae*, *Escherichia coli* and *S. aureus* was demonstrated in murine thigh and lung infection models.[22] Ceftaroline was found to be bacteriostatic for staphylococci and Gram-negative bacilli when free drug concentration exceeded the MIC for 30% and 40% of the dosing interval respectively. However, bactericidal activity for staphylococci and Gram-negative bacilli with ceftaroline occurred when percentage time >MIC was 50% and 60%, respectively.[22,23]

Table 2. Ceftaroline and Vancomycin Susceptibility Testing Results for Local MRSA Isolates[15-17]

Isolate	Year	MLST[a]	Vancomycin MIC (Etest), µg/mL	hVISA/ VISA[b]	Ceftaroline MIC (Etest), µg/mL	Ceftaroline MIC (Microbroth), µg/mL
1	2003	239	4	VISA	0.75	1.024
2	2005	239	0.75	-	1.0	1.024
3	2008	239	1	-	1.0	1.024
4	2006	239	1.5	-	0.75	1.024
5	2001	239	2	hVISA	1.0	1.024
6	2005	239	4	VISA	0.5	0.512
7	2009	239	3	VISA	0.75	1.024
8	2000	239	3	VISA	0.75	1.024
9	2007	239	2	hVISA	1.0	1.024
10	2005	239	2	-	0.75	1.024
11	2005	239	2	-	0.75	1.024
12	2006	239	2	-	1.0	1.024
13	2006	239	2	-	1.0	1.024
14	2008	239	2	-	1.0	1.024
15	2008	239	2	-	0.75	1.024
16	2009	239	2	-	1.0	1.024
17	2009	239	2	-	0.38	0.512
18	2010	239	2	-	1.0	1.024
19	2010	239	2	-	0.75	1.024
20	2010	239	2	-	1.0	1.024
21	2006	22	2	hVISA	0.75	0.512
22	2009	22	2	hVISA	0.75	1.024
23	2009	22	3	VISA	0.75	0.512
24	2005	22	0.75	-	1.0	1.024
25	2007	22	0.75	-	0.5	0.512
26	2004	22	1	-	0.75	1.024
27	2003	22	0.75	-	0.75	0.512
28	2007	22	1	-	0.75	0.512
29	2010	22	0.75	-	0.75	0.512
30	2010	22	0.5	-	0.75	0.512
31	2005	30	1	-	0.5	0.512
32	2007	30	0.75	-	0.75	0.512
33	2005	30	0.75	-	0.5	0.512
34	2005	30	0.75	-	0.75	0.512
35	2008	30	0.75	-	0.5	0.512
36	2003	80	1.5	-	0.38	0.512
37	2005	8	0.75	-	0.5	0.512
38	2004	59	1	-	0.38	0.512
39	2007	59	1	-	0.38	0.512
40	2005	398	1.5	-	0.38	0.512

[a]MLST: Multilocus sequence type. ST239 and ST22 are healthcare-associated MRSA; all others are community-associated MRSA except ST398, which is a livestock-associated MRSA.

[b]hVISA: Heterogeneous vancomycin-intermediate *S. aureus*; VISA: Vancomycin-intermediate *S. aureus*.

Table 3. Ceftaroline, Penicillin and Ceftriaxone Susceptibility Testing Results for Local *Streptococcus Pneumoniae* Isolates[18]

Isolate	Year	Sero-type	Penicillin MIC (Etest), µg/mL	Ceftriaxone MIC (Etest), µg/mL	Ceftaroline MIC (Etest), µg/mL	Ceftaroline MIC (Microbroth), µg/mL
1	2000	19F	1.5	0.75	0.125	0.128
2	2000	14	0.016	0.016	0.008	0.008
3	2000	20	0.016	0.023	0.012	0.008
4	2000	8	0.016	0.008	0.008	0.008
5	2000	9A/L	0.016	0.012	0.012	0.008
6	2000	12F	0.016	0.006	0.008	0.008
7	2000	8	0.016	0.012	0.012	0.008
8	2000	3	0.016	0.012	0.008	0.004
9	2001	14	0.75	0.38	0.125	0.128
10	2001	14	2	0.5	0.125	0.128
11	2001	7C	2	0.5	0.094	0.128
12	2001	NT[a]	0.016	0.06	0.008	0.004
13	2001	1	0.016	0.008	0.012	0.008
14	2001	20	0.016	0.016	0.008	0.008
15	2002	14	0.75	0.5	0.125	0.128
16	2002	1	1	0.138	0.094	0.064
17	2003	33F	1	0.5	0.125	0.256
18	2003	19F	1.5	0.5	0.19	0.256
19	2004	23F	2	1	0.125	0.128
20	2004	19F	2	1	0.125	0.128
21	2004	14	0.016	0.032	0.008	0.008
22	2004	33F	0.016	0.016	0.008	0.008
23	2004	6B	0.016	0.06	0.008	0.008
24	2005	3	0.016	0.016	0.008	0.004
25	2005	14	0.75	0.38	0.094	0.128
26	2005	6B	1	0.5	0.064	0.064
27	2005	14	1	0.12	0.094	0.129
28	2005	23F	2	1	0.125	0.128
29	2005	8	0.012	0.012	0.012	0.008
30	2005	NT[a]	0.016	0.016	0.012	0.008
31	2005	18C	0.016	0.008	0.008	0.008
32	2005	23F	0.016	0.016	0.006	0.008
33	2005	10A	0.016	0.016	0.008	0.004
34	2006	19F	1	0.5	0.094	0.128
35	2006	14	1.5	0.5	0.094	0.128
36	2010	6B	2	1	0.19	0.128
37	2007	19A	1	0.25	0.047	0.032
38	2007	23F	1	0.5	0.094	0.128
39	2007	23F	2	1	0.19	0.256
40	2007	19F	2	1	0.125	0.128

[a]NT: Non-typeable

Clinical Efficacy

The efficacy and safety of ceftaroline was assessed in 4 large phase 3 programmes of randomised, double-blind, clinical trials for CAP and cSSTI, and these are summarised in Table 4.[24-29]

The FOCUS 1 and 2[24,25] (ceFtarOline Community-acquired pneUmonia trial vS ceftriaxone in hospitalised patients) trials were the 2 pivotal trials used for registration with FDA for the indication of CAP. Similarly, the CANVAS 1 and 2[27,28] (CeftAroliNe Versus VAncomycin in Skin and Skin Structure Infections) trials were the 2 registration trials used for the indication of cSSTI.

The FOCUS programme was prospectively designed to pool results from both FOCUS 1 and 2 for integrated analysis as the 2 trials were similar to each other.[26] The primary objective was to determine non-inferiority in the clinical cure rates of ceftaroline compared with ceftriaxone in the clinically evaluable (CE) and modified intention-to-treat efficacy (MITTE) populations at the test-of-cure visit. The cure rates in both CE and MITTE populations met the non-inferiority criteria (lower limit of the 95% confidence interval being ≥ -10) but could not be considered superior to the comparator drugs in view of the design of the trials (Table 4).[26]

In the CANVAS studies, ceftaroline monotherapy was compared with vancomycin plus aztreonam in cSSTI. Similar to the FOCUS programmes, the 2 trials were designed to allow pooling of results for a larger database of pathogens and safety information.[29] The primary objective of each trial was also to determine non-inferiority of the clinical cure rate achieved with ceftaroline compared to vancomycin plus aztreonam combination therapy in the CE and MITTE patient populations. This was achieved. In a subgroup analysis, the clinical cure rates in microbiologically evaluable patients with MRSA were 93.45% and 94.3% in the ceftaroline and comparator arms respectively, but no confidence interval was reported.[29]

In summary, for the indications of CAP and cSSTI, therapy with ceftaroline was observed to be non-inferior to the comparator agents at both a standard test of cure assessment time (8 to 15 days after discontinuation of study drug) and an early assessment time point (day 3 or 4 of study). The recommended duration of therapy is 5 to 7 days and 5 to 14 days for CAP and cSSTI respectively.

Safety and Tolerability

Ceftaroline was generally well tolerated in the licensing trials, with an adverse event profile similar to the comparator agents—ceftriaxone and vancomycin plus aztreonam.[24,25,27,28] The most common adverse events reported in clinical trials were diarrhoea, nausea and headache and these are summarised in Table 4.[24-29]

Use of Ceftaroline for Other Indications

Currently, there is no clinical trial data available for use of ceftaroline out of its approved indications for CAP and cSSTI. A search on the clinical trials website (http://clinicaltrials.gov/) revealed 2 other studies on urinary tract infections and MRSA bacteremia respectively, but the results are not yet available. Nonetheless, there are numerous case reports/series on the use of ceftaroline for other infections, especially endocarditis. We have summarised these reports in Table 5.[30-34]

The anti-MRSA activity of ceftaroline has been exhibited in both in vitro and animal studies, including rabbit endocarditis models.[35,36]

In order to mitigate its vulnerability to extended-spectrum beta-lactamase-producing Enterobacteriaceae, ceftaroline has also been tested in combination with avibactam (formerly known as NXL104), a novel non-beta-lactam beta-lactamase inhibitor.[37-39] Avibactam permanently inactivates extended-spectraum beta-lactamases and *amp*C enzymes by forming a stable and irreversible covalent bond within their active sites.[40] The combination of ceftaroline and avibactam has demonstrated in vitro potency against extended-spectrum beta-lactamase- and *amp*C-producing Enterobacteriaceae, but not against *P. aeruginosa* or *Acinetobacter baumannii*.[37-39] It is currently being evaluated in Phase 2 studies of complicated urinary tract and intra-abdominal infections by AstraZenica/Forest.[41]

Clinical Limitations and Potential Usage of Ceftaroline (Especially Local Context)

Ceftaroline has only been rigorously tested on specific populations of patients with CAP and cSSTI in randomised controlled clinical trials,[24-29] and its clinical efficacy on other types of infections and also within CAP and cSSTI subpopulations remain uncertain. Much of its presumptive efficacy—as evidenced by the case reports and series (Table 5)[30-34]—has been extrapolated based on in vitro susceptibility testing and by its nature as a cephalosporin, where, as a class of antibiotics, extensive experience has been accumulated.

For the indication of CAP, the results from the FOCUS trials support the efficacy and safety of the drug in inpatients with CAP who are managed in a non-intensive care unit (ICU) setting, but its efficacy in other populations is not clear. Based on the exclusion criteria, data are lacking in patients that are immunosuppressed, require ICU admission, or have risk factors for other hospital-acquired infections. Importantly, ceftaroline demonstrated clinical efficacy for the treatment of multidrug-resistant *S. pneumoniae*, but larger studies are needed to confirm these findings. In the local and regional setting, where pneumonia caused by *Burkholderia pseudomallei* is a concern particularly in severely ill patients where early appropriate antibiotic

Table 4. Summary of Licensing Trials for Ceftaroline[24-29]

	FOCUS 1 and 2[24-26]		CANVAS 1 and 2[27-29]	
Drugs	Ceftaroline	Ceftriaxone	Ceftaroline	Vancomycin plus Aztreonam
Indication	Community-acquired pneumonia		Complicated skin and soft tissue infection	
Type of Trials	Phase III multicenter, randomised, double-blind		Phase III multicenter, randomised, double-blind	
Study design	To demonstrate non-inferiority of comparator		To demonstrate non-inferiorityof comparators	
Number of patients randomised	1240		1396	
Key exclusions	Patients • Admitted to the intensive care unit • On dialysis • With risk factors for an MRSA Infection (as ceftriaxone is not effective against this organism)		Patients with • Suspected *Pseudomonas aeruginosa* or anaerobic infection • Decubitus ulcer, diabetic foot ulcer, ulcer associated with peripheral vascular disease accompanied by osteomyelitis • Extensive burns	
Doses	600 mg IV every 12 hours	1g IV every 24 hours	600 mg IV every 12 hours	Vancomycin 1g IV every 12 hours plus aztreonam 1g IV every 8 hours
Clinical cure rates				
a) In clinically evaluable populations	387/459 (84.3%)	349/449 (77.7%)	559/610 (91.6%)	549/592 (92.7%)
	95% CI, 1.6 to 11.8		95% CI, – 4.2 to 2.0	
b) In modified intent-to-treat efficacy populations	479/580 (82.6%)	439/573 (76.6%)	595/693 (85.9%)	586/685 (85.5%)
	95% CI, 1.4 to 10.7		95% CI, – 3.4 to 4	
c) In microbiologically evaluable populations	131/154 (85.1%)	111/147 (75.5%)	434/468 (92.7%)	421/446 (94.4%)
	95% CI, 0.7 to 18.8		95% CI, – 4.9 to 1.6	
d) In community-acquired pneumonia caused by *Streptococcus pneumoniae*	59/69 (85.5%)	48/70 (68.8%)		
	No 95% CI reported			
e) In multidrug-resistant *S. pneumoniae* pneumonia	4/4 (100%)	2/9 (22%)		
f) In microbiologically evaluable patients with MRSA cSSTI			142/152 (93.4%)	115/122 (94.3%)
			No CI reported	
g) In MRSA bacteremia			6/7 (85.7%)	2/2 (100%)
			95% CI, – 53.5 to 58.4	
Treatment emergent adverse events				
a) Nausea (%)	2.3	2.3	5.9	5.1
b) Headache (%)	3.4	1.5	5.2	4.5
c) Rash (%)	NA	NA	3.2	2.5
d) Diarrhoea (%)	4.2	2.6	4.9	3.8
e) *Clostridium-difficle* associated diarrhoea	0	0	2 cases	1 case

CI: Confidence interval; NA: Not available

Table 5. Summary of Case Reports of Ceftaroline Used in Indications Other Than Cap And cSSTI[30-34]

Author of case reports	No. of patients	Type of Infection	Failed prior therapy (if any)	Indication for Ceftaroline	Highest dose of ceftaroline used	Clinical outcome[a, b]
Ho et al[30]	6	Persistent MRSA bacteremia • 2 endocarditis • 1 uveitis and endophalmitis • 1 UTI • 1 uveitis and ethmoid osteomyelitis • 1 prostatitis and septic thrombophlebitis	Vancomycin and/ or daptomycin	Salvage	600 mg 8H	5 achieved clinical cure; 6 achieved microbiological cure; 1 death
Lin et al[31]	10	• 4 MRSA bacteremia with probable endocarditis • 1 MRSA bacteremia with probable endocarditis and septic arthritis • 2 MRSA pneumonia • 1 MRSA bactermia with septic arthritis • 2 osteomylitis	Vancomycin and/ or daptomycin	Salvage and/or add on therapy to daptomycin	600 mg 8H (or lower for patients with impaired renal function)	6 achieved clinical cure; 7 achieved microbiological cure; 3 deaths
Rose et al[32]	1	Persistent MRSA bacteremia, septic shock and development of reduced daptomycin susceptibility	Daptomycin	Add on therapy to daptomycin	200 mg bd (adjusted for ESRF)	Achieved microbiological cure and discharged to hospice
Jongsma et al[33]	1	Persistent MRSA bacteremia and daptomycin-non-susceptible *Staphylococcus aureus* infective endocarditis and osteomyelitis	Daptomycin and vancomycin	Salvage	600 mg bd	Clinical and microbiological cure
Sakoulas G et al[34]	1	Recurrent case of left-sided endocarditis caused by high-level aminoglycoside-resistant *Enterococcus faecalis*	Ampicillin and ceftriaxone, followed by ampicillin and daptomycin	Add on therapy to daptomycin for synergy (ampicillin was discontinued)	600 mg 8H	Clinical and microbiological cure

[a]Clinical cure was defined as resolution of all signs and symptoms of infection or improvement such that no further antimicrobial therapy was necessary.
[b]Microbiological cure was defined as negative cultures after antimicrobial therapy.
UTI: Urinary Tract Infection

coverage may be critical, it is less easy to delineate a niche for ceftaroline, especially as the cost of the drug is high compared to standard CAP therapy. Existing in vitro susceptibility testing data on 30 isolates suggest that the *B. pseudomallei* ceftaroline MIC is equivalent to ceftazidime MIC,[42] but the dose required to attain the pharmacodynamic breakpoint (extrapolated to be 5 to 6 grams daily) is far higher than is currently recommended for CAP or that which has been tested in early human studies to date.

For the indication of cSSTI, its anti-MRSA activity increases the options for clinicians who may be able to use ceftaroline as a single agent for the treatment of mixed Gram-negative and Gram-positive (with MRSA) infections. However, ceftaroline does not have good in vitro activity against several important nosocomial Gram-negative pathogens such as *P. aeruginosa*. Thus it may not be an adequate substitute for currently used antibiotics such as ceftazidime, cefepime or piperacillin/tazobactam for the empiric treatment of nosocomial cSSTI, or as empirical treatment for any nosocomial infection locally. Ceftaroline will likely not become the first-line therapy for nosocomial cSSTI in the near future but is otherwise a viable alternative in the right setting, i.e. culture-directed therapy where only MRSA and susceptible Gram-negative bacteria are cultured out, and/or where vancomycin is not appropriate or has failed therapy.

Although not currently recommended as a treatment for MRSA bacteremia, this is the area where ceftaroline has the greatest potential to improve on current therapy. Other than daptomycin, beta-lactam antibiotics have generally proven superior to other classes of antibiotics for the treatment of *S. aureus* bacteremia and endocarditis.[43] Early data from case reports are promising, but a formal clinical trial is required to ascertain the role of ceftaroline for *S. aureus* (including MRSA) bacteremia. As this point in time, we would recommend that ceftaroline should only be prescribed

for patients with severe systemic MRSA infections who have already failed vancomycin and/or daptomycin therapy. More frequent dosing intervals (IV 600 mg 8H) is recommended based on pharmacodynamics parameters and the experiences reported in existing case reports.[30-34]

In terms of drug delivery, ceftaroline has to be provided via the intravenous route twice (or thrice) daily for patients with normal renal function. It therefore offers no advantage in terms of administration when compared with alternative agents, particularly for CAP (levofloxacin or moxifloxacin can be orally administered, whereas ceftriaxone can be administered intravenously once a day). Once reconstituted, the drug is only stable for 6 hours at room temperature (or 24 hours at 2 to 8 degrees Celsius).[3] Thus it has no role in terms of outpatient antibiotic therapy (OPAT).

Because ceftaroline has just been launched in Singapore and has not been included in any public hospital's drug formulary, local experience is limited and largely restricted to patients with disseminated MRSA infections who have failed more conventional therapy such as vancomycin and daptomycin. Anecdotally, success rates have been variable.

Conclusion

In summary, ceftaroline is the first cephalosporin to be approved for the treatment of MRSA infections with an efficacy profile similar to its comparators in the treatment of CAP and cSSTI. Its strength lies in this enhanced Gram-positive coverage. More research is necessary to determine its role in other severe systemic MRSA infections such as bacteremia and osteomyelitis. While its spectrum of activity is extensive in comparison to earlier-generation cephalosporins, inadequate coverage of non-fermenting Gram-negative bacteria such as *P. aeruginosa* and *A. baumannii*, and its vulnerability to extended-spectrum beta-lactamases produced by a significant proportion of local nosocomial Enterobacteriaceae restrict its usefulness as an antimicrobial agent for empirical treatment of healthcare-associated infections. In the local context, the high drug costs, uncertainty about coverage of *B. pseudomallei* and low rates of community-associated MRSA pneumonia[44] render it less appealing as empirical therapy for moderate-to-severe CAP. We anticipate that ceftaroline will occupy primarily niche roles for culture-directed treatment of various infections—in particular those caused by MRSA—until further clinical trial data become available.

Acknowledgments

The laboratory testing on local MRSA and Streptococcus pneumoniae isolates was funded by AstraZeneca. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Clinical and Laboratory Standards Institute. Performace Standards for Antimicrobial Susceptibility; 23rd informational supplement. CLST document M100-S23. Wayne PA: CLSI, 2013.
2. Kollef MH. New antimicrobial agents for methicillin-resistant Staphylococcus aureus. Crit Care Resusc 2009;11:282-6.
3. Drug Information Online. Ceftaroline fosamil. Available at: http://www.drugs.com/monograph/ceftaroline-fosamil.html. Accessed 13 August 2013.
4. UK Medicines Information. Available at: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4530. Accessed 12 August 2013.
5. Health Sciences Authority Singapore. Available at: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/New_Approval/Nov_2012.html. Accessed 12 August 2013.
6. Fuda C, Suvorov M, Vakulenko SB, Mobashery S. The basis for resistance to beta-lactam antibiotics by penicillin-binding protein 2a of methicillin-resistant Staphylococcus aureus. J Biol Chem 2004;279:40802-6.
7. Drusano GL. Pharmacodynamics of ceftaroline fosamil for complicated skin and skin structure infection: rationale for improved anti-methicillin-resistant Staphylococcus aureus activity. J Antimicro Chemother 2010;65 Suppl 4:33-9.
8. Laudano JB. Ceftaroline fosamil: a new broad-spectrum cephalosporin. J Antimicro Chemother 2011;66 Suppl 3:11-18.
9. Kosowski-Shick K, McGhee PL, Appelbaum PC. Affinity of ceftraoline and other beta-lactams for penicillin-binding proteins from Staphylococcus aureus and Strepotococcus pneumoniae. Antimicrob Agents Chemother 2010;54:1670-7.
10. Mushtaq S, Warner M, Ge Y, Kaniga K, Livermore DM. In vitro activity of ceftaroline (PPI-0903M, T-91825) against bacteria with defined resistance mechanisms and phenotypes. J Antimicrob Chemother 2007; 60:300-11.
11. Ge Y, Biek D, Talbot GH, Sahm DF. In vitro profiling of Ceftaroline against a collection of recent bacterial clinical isolates from across the United States. Antimicrob Agents Chemother 2008;52:3398-407.
12. Saravolatz LD, Stein GE, Johnson LB. Ceftaroline: A novel cephalosporin with activity against methicillin-resistant Staphylococcus aureus. Clin Infect Dis 2011;52:1156-63.
13. Steed M, Vidaillac C, Rybak MJ. Evaluation of ceftaroline nactivity versus daptomycin (DAP) against DAP-nonsusceptible methicillin-resistant Staphylococcus aureus strains in an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother 2011;55:3522-6.
14. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters Version 3.1. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_3.1.pdf. Accessed 24 July 2013.
15. Teo J, Tan TY, Hon PY, Lee W, Koh TH, Krishnan P, et al. ST22 and ST239 MRSA duopoly in Singaporean hospitals: 2006-2010. Epidemiol Infect 2013;141:153-7.
16. Hsu LY, Koh YL, Chlebicka NL, Tan TY, Krishnan P, Lin RT, et al. Establishment of ST30 as the predominant clonal type among community-associated methicillin-resistant Staphylococcus aureus isolates in Singapore. J Clin Microbiol 2006;44:1090-3.
17. Sergio DM, Koh TH, Hsu LY, Ogden BE, Goh AL, Chow PK. Investigation of methicillin-resistant Staphylococcus aureus in pigs used for research. J Med Microbiol 2007;56:1107-9.
18. Hsu LY, Lui SW, Lee JL, Hedzlyn HM, Kong DH, Shameen S, et al. Adult invasive pneumococcal disease pre- and peri-pneumococcal conjugate vaccine introduction in a tertiary hospital in Singapore. J Med Microbiol 2009;58:101-4.
19. Citron DM, Tyrrell KL, Merriam CV, Goldstein EJC. In Vitro activity of Ceftaroline against 623 diverse strains of anaerobic bacteria. Antimicrob Agents Chemother 2010;54:1627-32.

20. Zhanel GG, Sniezek G, Schweizer F, Zelenitsky S, Lagacé-Wiens PR, Rubinstein E et al. Ceftaroline: a novel broad spectrum cephalosporin with activity against meticillin-resistant Staphylococcus aureus. Drugs 2009;69:809-31.
21. Kanafani ZA, Corey GR. Ceftaroline: a cephalosporin with expanded gram-positive activity. Future Microbiol 2009;4:25-33.
22. 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.
23. Maselli DJ, Fernandez JF, Whong CY, Echevarria K, Nambiar AM, Anzueto A, et al. Clinical evaluation of the role of ceftaroline in the management of community acquired bacterial pneumonia. Infect Drug Resist 2012;5:43-51.
24. File TM, 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 3:19-32.
25. Low DE, File TM, 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 3:33-44.
26. File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis 2010;51:1395-405.
27. Corey GR, Wilcox MH, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:41-51.
28. Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:53-65.
29. Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010;51:641-50.
30. Ho TT, Cadena J, Childs LM, Ganzalez-Velez M, Lewis II JS . Methicillin-resistant Staphylococcus aureus bacteremia and endocarditis treated with ceftaroline salvage therapy. J Antimicrob Chemother 2012;67:1267-70.
31. Lin JC, Aung G, Thomas A, Jahng M, Johns S, Fierer J. The use of ceftaroline fosamil in methicillin-resistant staphylococcus aureus endocarditits and deep-seated MRSA infections: a retrospective case series of 10 patients. J Infect Chemother 2013;19:42-9.
32. Rose WE, Schulz LT, Andes D, Striker R, Berti AD, Hutson PR, et al. Addition of Ceftaroline to Daptomycin after emergence of Daptomycin-Nonsusceptible Staphylococcus aureus during therapy improves antibacterial therapy. Antimicrob Agents Chemother 2012;56:5296-302.
33. Jongsma K, Joson J, Heidari A. Ceftaroline in the treatment of concomitant methicillin-resistant and daptomycin-non-susceptible Staphylococcus aureus infective endocarditis and osteomyelitis: case report. J Antimicrob Chemother 2013;68:1444-5.
34. Sakoulas G, Nonejuie P, Nizet V, Pogliano J, Crum-Cianflone N, Haddad F. Treatment of High-Level Gentamicin-Resistant Enterococcus faecalis endocarditis with Daptomycin plus Ceftaroline. Antimicrob Agents Chemother 2013;57:4042-5.
35. Jacqueline C, Caillon J, Le Mabecque V, Miegeville AF, Hamel A, Bugnon D, et al. In vivo efficacy of ceftaroline (PPI-0903), a new broad-spectrum cephalosporin, compared with linezolid and vancomycin against methicillin-resistant and vancomycin-intermediate Staphylococcus aureus in a rabbit endocarditis model. Antimicrob Agents Chemother 2007;51: 3397-400.
36. Jacqueline C, Amador G, Batard E, Mabecque VL, Miegeville AF, Biek D, et al. Comparison of ceftaroline fosamil, daptomycin and tigecycline in an experimental rabbit endocarditis model caused by methicillin-susceptible, methicillin-resistant and glycopeptide-intermediate Staphylococcus aureus. J Antimicrob Chemother 2011;66:863-6.
37. Louie A, Castanheira M, Liu W, Grasso C, Jones RN, Williams G, et al. Pharmacodynamics of β-Lactamase Inhibition by NXL104 in combination with Ceftaroline: Examining organisms with multiple types of β-lactamases. Antimicrob Agents Chemother 2012;56:258-70.
38. Mushtaq S, Warner M, Williams G, Critchley I, Livermore DM. Activity of chequerboard combinations of ceftaroline and NXL104 versus β -lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2010;65:1428-32.
39. Karlowsky JA, Adam HJ, Baxter MR, Lagacé-Wiens PR, Walkty AJ, Hoban DJ, et al. In Vitro Activity of Ceftaroline-Avibactam Against Gram-Negative and Gram-Positive Pathogens Isolated from Patients in Canadian Hospitals in 2010-2012: Results from the CANWARD Surveillance Study. Antimicrob Agents Chemother 2013 Aug 26 [Epub ahead of print].
40. Satchrya T, Pechereau MC, Bruneau JM, Claudon M, Frere JM, Miossec C, et al. Mechanistic studies of the inactivation of TEM-1 and P99 by NXL104, a novel non-β-lactam β -lactamase inhibitor. Antimicrob Agents Chemother 2010;54:5132-8.
41. Boucher HW, Talbot GH, Benjamin Jr DK, Bradley J, Guidos RJ, Jones RH, et al. 10 × '20 Progress—Development of new drugs active against gram-negative bacilli: An update from the Infectious Diseases Society of America. Clin Infect Dis 2013;56:1685-94 .
42. US Food and Drug Administration. Ceftaroline for injection. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200327Orig1s000MicroR.pdf. Accessed 13 August 2013.
43. Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med 2006;355:653-65.
44. Wijaya L, Hsu LY, Kurup A. Community-associated methicillin-resistant Staphylococcus aureus: overview and local situation. Ann Acad Med Singapore 2008;35:479-86.