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Ceftaroline

A Novel Broad-Spectrum Cephalosporin with Activity against Meticillin-Resistant *Staphylococcus aureus*

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Abstract

Ceftaroline is a broad-spectrum cephalosporin currently under clinical investigation for the treatment of complicated skin and skin-structure infections (cSSSI), including those caused by meticillin-resistant *Staphylococcus aureus* (MRSA), and community-acquired pneumonia (CAP). Ceftaroline has the ability to bind to penicillin-binding protein (PBP)2a, an MRSA-specific PBP that has low affinity for most other β-lactam antibacterials. The high binding affinity of ceftaroline to PBP2a (median inhibitory concentration 0.90 μg/mL) correlates well with its low minimum inhibitory concentration for MRSA. Ceftaroline is active *in vitro* against Gram-positive cocci, including MRSA, meticillin-resistant *Staphylococcus epidermidis*, penicillin-resistant

Streptococcus pneumoniae and vancomycin-resistant *Enterococcus faecalis* (not *E. faecium*). The broad-spectrum activity of ceftaroline includes many Gram-negative pathogens but does not extend to extended-spectrum β-lactamase-producing or AmpC-derepressed Enterobacteriaceae or most nonfermentative Gram-negative bacilli. Ceftaroline demonstrates limited activity against anaerobes such as *Bacteroides fragilis* and non-fragilis *Bacteroides* spp. Limited data show that ceftaroline has a low propensity to select for resistant subpopulations.

Ceftaroline fosamil (prodrug) is rapidly converted by plasma phosphatases to active ceftaroline. For multiple intravenous doses of 600 mg given over 1 h every 12 hours for 14 days, the maximum plasma concentration was 19.0 μg/mL and 21.0 μg/mL for first and last dose, respectively. Ceftaroline has a volume of distribution of 0.37 L/kg (28.3 L), low protein binding (<20%) and a serum half-life of 2.6 hours. No drug accumulation occurs with multiple doses and elimination occurs primarily through renal excretion (49.6%). Based on Monte Carlo simulations, dosage adjustment is recommended for patients with moderate renal impairment (creatinine clearance 30–50 mL/min); no adjustment is needed for mild renal impairment.

Currently, limited clinical trial data are available for ceftaroline. A phase II study randomized 100 patients with cSSSI to intravenous ceftaroline 600 mg every 12 hours or intravenous vancomycin 1 g every 12 hours with or without intravenous aztreonam 1 g every 8 hours (standard therapy) for 7–14 days. Clinical cure rates were 96.7% for ceftaroline compared with 88.9% for standard therapy. Adverse events were similar between groups and generally mild in nature. In a phase III trial, 702 patients with cSSSI were randomized to ceftaroline 600 mg or vancomycin 1 g plus aztreonam 1 g, each administered intravenously every 12 hours for 5–14 days. Ceftaroline was noninferior to vancomycin plus aztreonam in treating cSSSI caused by both Gram-positive and -negative pathogens. Adverse event rates were similar between groups.

Ceftaroline is well tolerated, which is consistent with the good safety and tolerability profile of the cephalosporin class. In summary, ceftaroline is a promising treatment for cSSSI and CAP, and has potential to be used as monotherapy for polymicrobial infections because of its broad-spectrum activity. Further clinical studies are needed to determine the efficacy and safety of ceftaroline, and to define its role in patient care.

Multidrug-resistant pathogens, such as meticillin-resistant *Staphylococcus aureus* (MRSA), are becoming more prevalent in both the hospital and community settings. According to the Centers for Disease Control and Prevention (CDC), approximately 19 000 deaths occur annually from invasive (severe) MRSA infections.[1] In the US, hospitals have observed a rapid rise in MRSA, with healthcare-associated (HA)-MRSA infections in intensive care units having risen from 2% in 1974 to 64% in 2005.[1,2] In Canada, the incidences of HA-MRSA and community-associated (CA)-MRSA infections have been steadily increasing since the first reported case of MRSA in 1981.[3] In 2006, the Canadian Nosocomial Infection Surveillance Program reported an overall incidence rate of 8.04 cases of MRSA per 1000 patients admitted to Canadian hospitals.[4] Considering this rate was 5.10 cases per 1000 patients in 2003, it is clear that resistance is on the rise for this pathogen.[5] Similarly high rates have been reported by the European Antimicrobial Resistance Surveillance System, although the prevalence of MRSA varied by region from <1% in

northern Europe to >40% in southern and western Europe.[6] Regardless of geographical location, MRSA is difficult to treat and clinicians have limited antibacterial options.

Typical first-line treatment of MRSA infection includes vancomycin or linezolid. However, these antibacterials have limitations. Decreased susceptibility or resistance to vancomycin has emerged with vancomycin-intermediate *S. aureus* (VISA – also called glycopeptide-intermediate *S. aureus* [GISA]; these terms are used interchangeably), hetero-resistant vancomycin-intermediate *S. aureus* (hVISA) and vancomycin-resistant *S. aureus* (VRSA).[7] Higher vancomycin trough concentrations are recommended to improve penetration for *S. aureus* infections, which would also increase the need for monitoring.[8] Although linezolid is highly active against MRSA, it is bacteriostatic and associated with potentially severe adverse effects, including thrombocytopenia and myelosuppression, and should be administered with another agent if Gram-negative pathogens are suspected.[9,10]

Complicated skin and skin-structure infections (cSSSI), more common in patients with diabetes mellitus, peripheral vascular disease and other co-morbid conditions, often require coverage for MRSA as well as Gram-negative pathogens.[11] Although the therapeutic options for these complicated infections are increasing,[11-13] there remains a need for continued development of effective antibacterials to combat resistant pathogens.

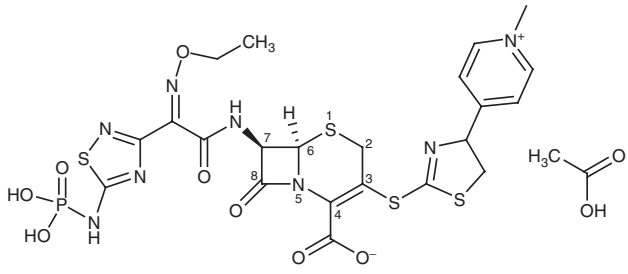
Ceftaroline fosamil is a novel, broad-spectrum cephalosporin exhibiting bactericidal activity against Gram-positive organisms, including MRSA and multidrug-resistant *Streptococcus pneumoniae* (MDRSP), as well as common Gram-negative pathogens. Ceftaroline is currently in phase III development for the treatment of cSSSI, including those caused by MRSA, and community-acquired pneumonia infections.[11,14] Promising results were seen in a phase II trial of ceftaroline compared with standard treatment (vancomycin ± aztreonam) for cSSSI, with clinical cure and microbiological success seen in 96.7% and 95.2%, respectively, of the ceftaroline-treated patients compared with 88.9% and 85.7%, respectively, of patients receiving standard therapy.[11] Similar results were demonstrated in a large phase III trial (CANVAS I) that included more than 700 patients, confirming the efficacy of ceftaroline for treatment of cSSSI.[15] Ceftaroline is being developed by Forest Laboratories, Inc. (New York, NY, USA).

This article reviews the available data on ceftaroline, including chemistry, mechanism of action, resistance, microbiology, pharmacokinetic and pharmacodynamic properties, and efficacy and safety in animal and clinical trials. A comprehensive literature search was performed using MEDLINE to identify articles on ceftaroline. Scientific meetings from 2003 to November 2008 were also searched for data on ceftaroline. The internet was accessed for additional information as needed.

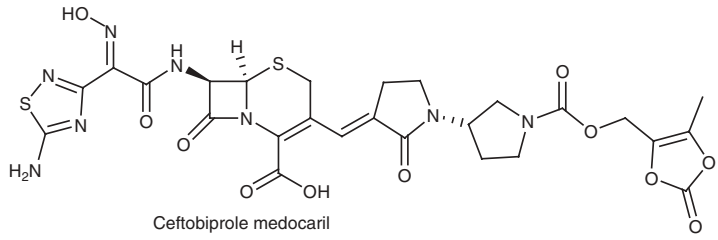
1. Chemistry

The essential structural component of a cephalosporin is a bicyclic ring system composed of a four-membered β-lactam ring fused with a six-membered dihydrothiazine (cephem) ring that includes a carbon double bond between positions 3 and 4. Variations on the 7-acylamino side chain and substitutions on the cephem ring have yielded a variety of cephalosporin compounds with different activity profiles.[16] The chemical structure of ceftaroline (figure 1) is related to cefozopran, a cephalosporin available outside of the US, with a zwitterion with a positively charged substituent at the 3-position and a negatively charged carboxyl group at the 4-position of the cephem ring.[16-18] At present, ceftaroline and ceftobiprole have been placed in a separate and unnamed subclass of the parenteral cephem class by the Clinical and Laboratory Standards Institute (CLSI).

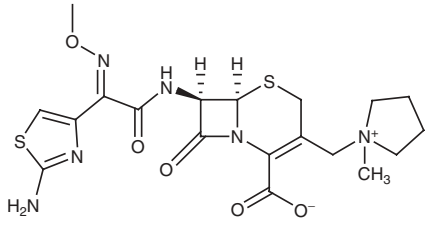
The *in vitro* and *in vivo* activity of ceftaroline can be rationalized by various structure-activity relationship concepts (figure 2). The oxime group preserved in third-generation (e.g. cefotaxime, ceftriaxone and ceftazidime) and fourth-generation (e.g. cefepime) cephalosporins is retained in ceftaroline and ceftobiprole, and is known to contribute to stability in the presence of β-lactamases.[19] The 1,2,4-thiadiazole ring present in all of these cephalosporins provides



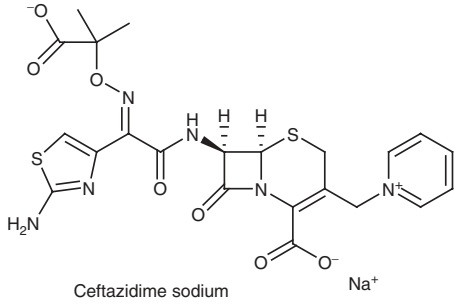
Ceftaroline fosamil (acetate)



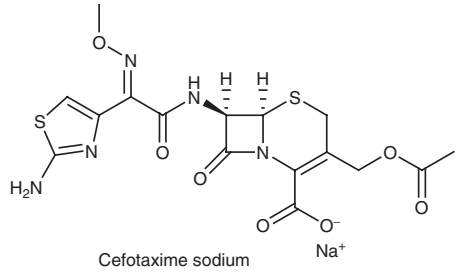
Ceftobiprole medocaril



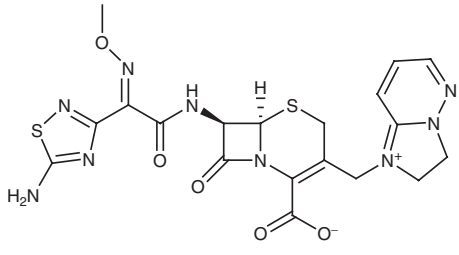
Cefepime



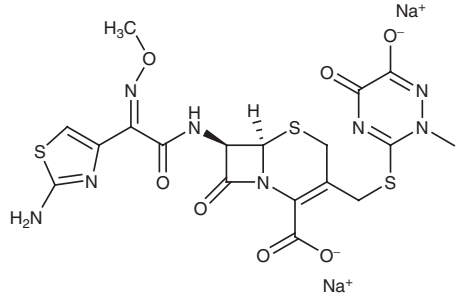
Ceftazidime sodium



Cefotaxime sodium



Cefozopran



Ceftriaxone disodium

Fig. 1. Chemical structures of ceftaroline fosamil (acetate), ceftobiprole medocaril, cefepime, ceftazidime sodium, cefotaxime sodium, cefozopran and ceftriaxone disodium.

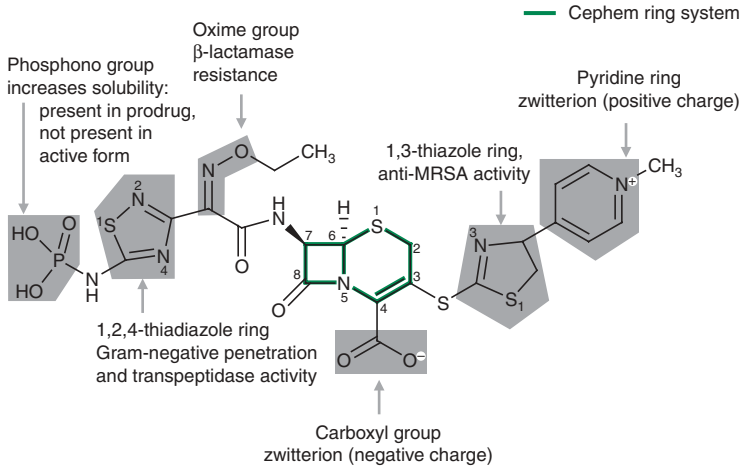


Fig. 2. Structure activity relationships for ceftaroline. **MRSA** = meticillin-resistant *Staphylococcus aureus*.

Gram-negative penetration and transpeptidase affinity, which prevents bacterial wall synthesis.[16] Additionally, the 1,3-thiazole ring attached to the 3-position of the cephem ring through a sulfur linker is believed to be a key structural motif contributing to the anti-MRSA activity of ceftaroline. The substituents on the 7-acylamino side chain of ceftaroline are analogous to those of cefozopran, with the exception of the phosphono group on the amino moiety of the 1,2,4-thiadiazole ring of ceftaroline.[18] The addition of this phosphono group significantly increases the water solubility of ceftaroline, allowing for conventional parenteral preparation and stability in the hospital setting.[17] Details of the chemical synthesis of ceftaroline have been described elsewhere.[18,20]

2. Mechanism of Action

A two-step process is involved in peptidoglycan synthesis inhibition by β-lactam antibacterials (equation 1). β-Lactams, including cephalosporins, inhibit bacterial cell-wall synthesis by mimicking the terminal acyl-D-Ala-D-Ala portion of the peptidoglycan peptide chain, resulting in acylation of a serine residue in the active site of the transpeptidase enzyme (also known as penicillin-binding proteins [PBPs]).[18,21] First, a noncovalent complex (EI) is formed between the antibacterial and the active site of the PBP, followed by the acylation of the active site (E-I). For maximal effectiveness, the disassociation constant (K_d) for the complex should be low, the rate of acylation (k_2) is high and the deacylation rate (k_3) is low. This produces efficient and irreversible inhibition of peptidoglycan synthesis and results in microbial death.[21]

$$E + I \overset{K_d}{\rightleftarrows} EI \overset{k_2}{\rightarrow} E - I \overset{k_3}{\rightarrow} E + P \qquad \text{(Eq. 1)}$$

MRSA isolates have acquired an additional PBP gene known as *mecA* that encodes PBP (referred to as PBP2′ or PBP2a), which is not inhibited by most β-lactam antibacterials. The ability of PBP2a to function in the presence of β-lactams allows cell-wall biosynthesis to continue, thus conferring resistance to most members of this antibacterial class.[21] However, ceftaroline has the ability to bind to PBP2a, demonstrating superior affinity (median inhibitory concentration [IC_{50}] = 0.90 μg/mL) as compared with cefozopran and other β-lactams.[18] The high affinity of ceftaroline for *S. aureus* PBPs correlates well with its low minimum inhibitory concentration (MIC) for MRSA or meticillin-susceptible *S. aureus* (MSSA) strains.[22]

The kinetic binding profile of ceftaroline is superior to that of imipenem or the cephalosporin nitrocefin. Villegas-Estrada et al.[21] measured the rate constants K_d, k_2 and k_3 for imipenem,

nitrocefin and ceftaroline for PBP2a transpeptidase in the presence of varying concentrations of a synthetic analogue of the repeat units of peptidoglycan (compound 1). It has been hypothesized that compound 1 mimics the action of a cell-wall component that binds to an allosteric site present in PBP2a, thus facilitating a more open conformation of the active site and allowing access by the β-lactam inhibitor.[23] As concentrations of compound 1 increased, k_2 increased and K_d decreased for all three antibacterials tested. In the presence of 0.5 mmol/L of compound 1, ceftaroline exhibited k_2 of 10×10^3/sec and K_d of 210 nmol/L compared with imipenem ($k_2=12\times10^3$/sec; $K_d=270\times10^3$ nmol/L) and nitrocefin ($k_2=15\times10^3$/sec; $K_d=135\times10^3$ nmol/L). Second-order rate constants (k_2/K_d) for imipenem and nitrocefin in the absence of compound 1 were <20 mol/L/sec, demonstrating an inefficient reaction. In contrast, the k_2/K_d for ceftaroline was $>10^4$ mol/L/sec, approximately 3-fold greater than the comparators. The effect of compound 1 on activity of ceftaroline was small, suggesting that ceftaroline itself is able to efficiently bind the allosteric site of PBP2a, thereby allowing direct access to the catalytic site where it exerts its inhibitory effect. Additionally, the PBP2a complexes with imipenem and nitrocefin both underwent deacylation (albeit slowly), whereas no k_3 value could be detected for ceftaroline, even after 96 hours of monitoring.[21]

3. Resistance

Studies of the propensity of ceftaroline to select for resistant subpopulations have been carried out with a number of Gram-positive and Gram-negative species.[24,25] Hinshaw et al.[25] evaluated the potential for development of resistance to ceftaroline *in vitro* with both Gram-positive and -negative pathogens. The spontaneous mutational frequency of 11 different Gram-positive and -negative pathogens was evaluated by inoculating agar containing ceftaroline at multiples of the MIC with 10^8–10^{10} colony-forming units (cfu). Resistance development during serial exposure was also assessed with a microbroth dilution method, by transferring cells from wells containing the highest concentration showing growth (usually one well below the MIC) to fresh media and repeating for a total of ten serial passages. MSSA, MRSA, CA-MRSA, VISA, penicillin-susceptible *S. pneumoniae* (PSSP), penicillin-resistant *S. pneumoniae* (PRSP) and β-lactamase-negative *Haemophilus influenzae* did not develop detectable resistance to ceftaroline using either method (frequency of spontaneous resistance $\leq10^{-8}$ for *H. influenzae*, PSSP and PRSP, and $\leq10^{-9}$–10^{-10} for MSSA and MRSA). Vancomycin-susceptible *Enterococcus faecalis* had a spontaneous mutation rate of 1.25×10^{-7} to ceftaroline at 4 times the MIC, but resistant colonies were not detected at 8 times or greater MIC. Spontaneous resistance to ceftaroline was not detected for vancomycin-resistant *E. faecalis*.

Mushtaq et al.[24] studied the *in vitro* activity of ceftaroline against clinical isolates and laboratory strains with known resistance mechanisms using both single-step and multi-step mutant selection. In the single-step mutant selection, which used ceftaroline at 4 times the MIC, there was a failure to select mutants at detectable frequencies from any of the three *S. aureus* strains tested (MSSA [$<2.82\times10^{-8}$], epidemic MRSA {EMRSA}-15 [$<2.74\times10^{-10}$] and VISA-Mu50 [$<5.88\times10^{-10}$]), PSSP ($<1.08\times10^{-8}$), PRSP ($<3.6\times10^{-7}$), and amoxicillin-susceptible ($<4.0\times10^{-9}$) and -resistant *H. influenzae* ($<3.3\times10^{-9}$). Two strains of *Enterobacter cloacae* (AmpC-inducible 684 and E827) gave rise to resistant mutants with ceftaroline and cefotaxime at frequencies between 10^{-7} and 10^{-8}. These mutants remained resistant in the presence of the extended-spectrum β-lactamase (ESBL) inhibitor clavulanic acid. Mutants of the TEM-containing *Escherichia coli* isolates 1411 pT1 and 1413 pT1 (hypermutable *mutS* derivative) were also observed with ceftaroline. After repeated passage on drug-free agar, only *E. coli* 1413 pT1 derivatives retained resistance to ceftaroline, perhaps resulting from mutations that occurred in this mismatch repair-deficient strain. These mutants, which exhibited unchanged MICs for cefotaxime, ceftriaxone and ceftazidime, regained susceptibility to ceftaroline in the presence of clavulanic acid.

In the multi-step mutant selection, 14 passages were performed using increasing concentrations of ceftaroline.[24] Elevated MIC values for ceftaroline could not be obtained from the three *S. aureus* strains (MSSA, EMRSA-15 and VISA-Mu50) tested. In contrast, increases in the ceftaroline MIC were observed against the TEM-β-lactamase-negative *E. coli* strain (from 0.06 to 1 mg/L) and the TEM-1 producer *E. coli* strain (0.25–128 mg/L). Different mechanisms were suggested to account for the ceftaroline resistance developed by the TEM-negative and TEM-1-producer *E. coli* mutants. The small increases in MIC against the TEM-negative mutants were observed with β-lactams (ceftaroline and other cephalosporins) and non-β-lactams (levofloxacin), suggesting up-regulated efflux and/or decreased permeability as mechanisms of resistance. Conversely, the TEM-1 producer mutants expressed a ceftazidime-resistant phenotype and strong ceftaroline/clavulanic acid synergy with little effect on levofloxacin MIC, consistent with an ESBL phenotype.

Gram-negative resistance to ceftaroline may most often reflect the ability of an organism to produce β-lactamases that hydrolyze the drug. In the study conducted by Mushtaq et al.,[24] ceftaroline retained good activity against isolates expressing classic TEM/SHV β-lactamases, but MICs were much higher for those with ESBLs, particularly isolates with TEM-3 or higher, SHV-2 or higher, or CTX-M. As expected, such resistant strains become sensitive to ceftaroline in the presence of clavulanic acid. For example, ESBL-producing *E. coli* raised the geometric mean ceftaroline MIC value from 0.046 to 32 mg/L, which was reduced by 0.1 mg/L by clavulanic acid.[24] Strains expressing class B metallo-β-lactamases are known to hydrolyze cephalosporins, including ceftaroline. *Klebsiella oxytoca, Proteus vulgaris* and *Pseudomonas aeruginosa,* which may produce cephalosporinases that hydrolyze ceftaroline, also showed increased MICs to ceftaroline.

In summary, ceftaroline exhibits potent activity against Gram-positive organisms, including MRSA and MDRSP. Ceftaroline has activity against many Gram-negative pathogens, including members of the Enterobacteriaceae, although it is not active against isolates producing ESBL or overexpressed AmpC enzymes. Slight lability to classic TEM and SHV β-lactamases and more significant resistance in ESBL-producing Enterobacteriaceae was reversible with clavulanic acid.

4. Microbiology

The *in vitro* antimicrobial activity of ceftaroline against Gram-positive and Gram-negative bacteria is presented in tables I and II.[24,26-40] To provide the broadest representation of ceftaroline activity to date, data were pooled from published *in vitro* studies of ceftaroline. Comparator data were pooled from the same published studies of ceftaroline, when comparative data were available. The MIC (mg/L) of 50% and 90% of isolates (MIC_{50} and MIC_{90}, respectively) and the MIC range for each listed organism are as reported by the study with the greatest number of isolates for that organism compared with the other studies.

Ceftaroline has excellent activity against MSSA, with MIC_{90} values 16- to 32-fold lower than those of ceftriaxone and ceftazidime, respectively (table I).[24,26-31,33,35-39] The MIC_{90} of ceftaroline against MRSA is >32-fold lower than ceftriaxone. Additionally, ceftaroline has demonstrated activity against *S. aureus* strains nonsusceptible to other antibacterial agents.[36,41,42] In a pharmacokinetic/pharmacodynamic model of human pharmacokinetics, ceftaroline demonstrated greater activity compared with vancomycin against one clinical MRSA and one hVISA strain, and equivalent activity to a second clinical MRSA isolate.[41] In a recent *in vitro* study, ceftaroline was bactericidal against clinical isolates of CA-MRSA, VISA, VRSA and daptomycin-nonsusceptible *S. aureus*, with MIC and minimum bactericidal concentration (MBC) values equal to or lower than those of vancomycin, daptomycin, linezolid, clindamycin, ceftriaxone and cotrimoxazole (sulfamethoxazole/trimethoprim).[42] Unlike ceftriaxone and ceftazidime, ceftaroline retains activity against meticillin-resistant strains of *S. epidermidis* (MIC_{90} = 1 mg/L) [table I].[30] Ceftaroline is moderately active against *E. faecalis* (MIC_{50} = 2 mg/L; MIC_{90} = 8 mg/L), but not

Table I. *In vitro* activity of ceftaroline and comparators against Gram-positive aerobic bacteria[29,30,36,37]

Bacteria, number of isolates	Ceftaroline			Ceftazidime		Ceftriaxone		Reference
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	
Staphylococcus aureus (MS), 1554	0.25	0.25	≤0.008–1	NA	NA	4	4	37
S. aureus (MR), 1237	1	1	0.25–2	NA	NA	32	>32	37
S. aureus (hVISA and VISA), 100	1	2	0.25–4	NA	NA	>32	>32	36
S. epidermidis (MS), 15	0.13	0.13	0.06–0.13	4	8	1	2	30
S. epidermidis (MR), 26	0.5	1	0.25–1	32	64	32	64	30
Enterococcus faecalis, 613	2	8	0.12 to >16	NA	NA	>32	>32	37
E. faecium (VAN-R), 26	>16	>16	4–16	>32	>32	>32	>32	29
Streptococcus pneumoniae (PS), 202	≤0.008	0.015	≤0.008–0.12	≤1	≤1	0.03	0.06	29
S. pneumoniae (PI), 103	0.015	0.06	≤0.008–0.5	2	8	0.12	0.5	29
S. pneumoniae (PR), 296	0.12	0.12	≤0.008–0.5	16	32	1	2	29
Viridans group streptococci (PS), 190	0.03	0.06	≤0.008–1	NA	NA	≤0.25	0.5	37
Viridans group streptococci (PR), 42	0.03	0.5	≤0.008–1	NA	NA	≤0.25	8	37
S. pyogenes (ERY-S), 91	≤0.008	≤0.008	≤0.008–0.03	≤1	≤1	≤0.015	0.03	29
S. agalactiae (ERY-S), 59	0.015	0.015	≤0.008–0.06	≤1	≤1	0.06	0.12	29
S. agalactiae (ERY-NS), 42	0.015	0.015	≤0.008–0.12	≤1	≤1	0.06	0.12	29

ERY-NS = erythromycin-nonsusceptible; **ERY-S** = erythromycin-susceptible; **hVISA** = hetero-resistant vancomycin-intermediate *S. aureus*; **MIC_{50}** = minimum inhibitory concentration (mg/L) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration of 90% of isolates; **MR** = meticillin-resistant; **MS** = meticillin-susceptible; **NA** = not available/assessed in study from which data for this pathogen is reported; **PI** = penicillin-intermediate; **PR** = penicillin-resistant; **PS** = penicillin-susceptible; **VAN-R** = vancomycin-resistant; **VISA** = vancomycin-intermediate *S. aureus*.

against *E. faecium* (MIC_{50} = 16 mg/L; MIC_{90} ≥32 mg/L).[24,26-31,33,35-39]

Ceftaroline exhibits potent activity against *S. pneumoniae*. As observed with other cephalosporins, the *in vitro* activity of ceftaroline against *S. pneumoniae* varies according to the penicillin susceptibility of the isolates. The MIC_{90} values of ceftaroline against penicillin-susceptible, -intermediate and -resistant strains of *S. pneumoniae* (0.015 mg/L, 0.06 mg/L and 0.12 mg/L, respectively) are lower than those of ceftazidime and ceftriaxone (table I). In a recent study,[43] ceftaroline was noted to be highly active against penicillin-, amoxicillin-, cefuroxime- and cefotaxime-resistant strains of *S. pneumoniae*. The ceftaroline MIC_{90} against these resistant strains was 0.25 mg/L, which was at least 8-fold lower than those of penicillin, cefotaxime or cefepime. The susceptibility to ceftaroline was greatest among all cephalosporins tested in the study (ceftriaxone, cefotaxime, cefuroxime and cefepime), including isolates of the increasingly prevalent serotype 19A (MIC_{90} = 0.25 mg/L). McGee et al.[32] examined the activity of ceftaroline against a collection of 120 highly cephalosporin-resistant clinical isolates of *S. pneumoniae* from the CDC. Comparators included cefotaxime, penicillin, ceftriaxone, amoxicillin and meropenem. The MIC_{90} for ceftaroline against this collection of resistant isolates was 0.5 mg/L and the highest MIC observed was 2 mg/L (for a single isolate). In contrast, the MIC_{90} values of 8 mg/L for cefotaxime, ceftriaxone, penicillin and >8 mg/L for amoxicillin were 16-fold higher than that for ceftaroline, and that for meropenem was 4-fold higher. This potent *in vitro* activity of ceftaroline was extended to a set of 18 *S. pneumoniae* laboratory-derived strains of R6 containing defined *pbp* and *murM* mutations

Table II. *In vitro* activity of ceftaroline and comparators against Gram-negative aerobic bacteria[29,30,36,38,40]

Bacteria, number of isolates	Ceftaroline			Ceftazidime		Ceftriaxone		Cefepime		Reference
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	
Haemophilus influenzae (BL-neg), 305	≤0.008	0.015	≤0.008–0.25	NA	NA	≤0.25	≤0.25	NA	NA	38
H. influenzae (BL-pos), 101	0.015	0.03	≤0.008–2	0.06	0.12	≤0.06	≤0.06	0.06	0.12	29
Moraxella catarrhalis (BL-pos), 93	0.06	0.25	≤0.03–0.5	≤1	≤1	≤0.25	1	ND	ND	29
Neisseria gonorrhoeae, 403	0.125	0.25	0.002–1	ND	ND	0.008	0.03	ND	ND	40
Escherichia coli (CAZ-S), 345	0.06	0.5	≤0.03 to >16	0.12	0.25	≤0.06	0.12	≤0.03	0.12	29
E. coli (CAZ-NS), 63	>16	>16	2 to >16	>32	>32	>16	>16	2	>32	29
E. coli (ESBL), 15	>32	>32	0.5 to >32	8	>16	>32	>32	16	>16	36
Klebsiella oxytoca, 19	0.25	2	0.03 to >128	0.13	2	0.06	32	ND	ND	30
K. pneumoniae, 210	0.06	0.25	≤0.03 to >16	0.12	0.25	≤0.06	0.12	≤0.03	0.12	29
K. pneumoniae (ESBL), 15	>32	>32	32 to >32	>16	>16	>32	>32	8	>16	36
Proteus mirabilis, 58	0.06	4	≤0.03 to >16	0.06	0.12	≤0.06	0.12	0.06	0.5	29
Serratia marcescens, 59	0.5	16	0.12 to >16	0.12	1	0.25	4	0.06	0.5	29
Salmonella spp., 46	0.13	0.25	0.13–2	0.25	0.5	0.13	0.13	ND	ND	30
Citrobacter freundii (CAZ-S), 50	0.12	0.25	0.06–16	0.25	1	0.12	0.5	≤0.03	0.12	29
C. freundii (CAZ-NS), 33	>16	>16	4 to >16	>32	>32	>16	>16	1	4	29
Enterobacter cloacae (CAZ-S), 50	0.12	1	≤0.03 to >16	0.25	1	0.12	1	0.06	0.12	29
E. cloacae (CAZ-NS), 35	>16	>16	0.12 to >16	>32	>32	>16	>16	1	4	29
Acinetobacter spp., 47	4	>16	≤0.03 to >16	4	>32	16	>16	4	32	29
Pseudomonas aeruginosa, 58	16	128	1 to >128	2	32	32	>128	ND	ND	30
Stenotrophomonas maltophilia, 10	>32	>32	32 to >32	8	>16	>32	>32	16	>16	36

BL-neg = β-lactamase-negative; **BL-pos** = β-lactamase-positive; **CAZ-NS** = ceftazidime-nonsusceptible; **CAZ-S** = ceftazidime-susceptible; **ESBL** = extended-spectrum β-lactamase; **MIC_{50}** = minimum inhibitory concentration (mg/L) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration of 90% of isolates; **NA** = not available/assessed in study from which data for this pathogen is reported; **ND** = no data available.

conferring resistance to β-lactams. Against this collection, which included isolates with ceftriaxone MIC values of up to 8 mg/L, the highest ceftaroline MIC was only 0.25 mg/L, suggesting that ceftaroline may overcome existing mechanisms of target-mediated β-lactam resistance. In a study by Patel et al.,[39] a collection of 219 MDRSP isolates from the Canadian Bacterial Surveillance Network were tested against seven antibacterials, including ceftaroline (MIC_{90} = 0.25 mg/L) and ceftobiprole (MIC_{90} = 1 mg/L). Multidrug resistance was defined as resistance to two or more classes of drugs. The MIC_{90} values for ceftaroline, ceftobiprole, ceftriaxone and amoxicillin were 0.25 mg/L (range 0.03–0.5 mg/L), 1 mg/L (range 0.03–2.0 mg/L), 2 mg/L (0.25–8 mg/L) and 8 mg/L (0.06–16 mg/L), respectively, for the MDRSP isolates. Cethromycin was the most active agent with an MIC_{90} of 0.12 mg/L (range 0.03–4 mg/L), which was 2-fold lower than that for ceftaroline. Among the β-lactams tested, ceftaroline was the most active, with MIC_{90} values 8-fold lower than ceftriaxone and 4-fold lower than ceftobiprole. The activity of ceftaroline against other streptococci (viridans group [MIC_{90} = 0.06 mg/L], *S. pyogenes* [MIC_{90} ≤0.008 mg/L] and *S. agalactiae* [MIC_{90} = 0.015 mg/L]) is also notable[29,30] (table I).

The spectrum of activity of ceftaroline against Gram-negative bacteria resembles that of the extended-spectrum cephalosporins (table II).[24,26-31,36-38,40] Ceftaroline demonstrates potent activity against *H. influenzae* (including β-lactamase-positive isolates), ceftazidime-susceptible *E. coli* and non-ESBL-producing *Klebsiella pneumoniae* similar to that of ceftriaxone, ceftazidime and cefepime (table II). Ceftaroline alone is not considered active against *P. aeruginosa* or ceftazidime-resistant Gram-negative pathogens such as ESBL producers, which may be considered beneficial for minimizing the emergence of resistant strains.

There are limited data available on the *in vitro* activity of ceftaroline against anaerobes. In a study by Sader et al.,[36] ceftaroline showed marginal activity against *Clostridium difficile* and slightly higher activity against other *Clostridium* species. The MIC_{90} of ceftaroline against both *Bacteroides fragilis* and *Prevotella* spp. was ≥32 mg/L. Activity against other Gram-positive anaerobes ranged from 0.03 to 0.12 mg/L based on data from 14 strains including two *Proprionibacterium acnes* strains, nine *Proprionibacterium* spp. strains and three *Peptostreptococcus* spp. strains.

Ceftaroline demonstrated bactericidal activity at or 1 $\log_2$ dilution above the MIC for 86.3% of 110 organisms tested, and 90% of strains had an MBC/MIC ratio of ≤4 (preferred ratios).[44] Seventeen strains (six *S. aureus*, two *S. epidermidis*, four *S. pneumoniae,* and one each of *E. coli, K. pneumoniae, H. influenzae*, *Serratia marcescens* and *E. cloacae*) were tested by kill-curve methodology to determine the bactericidal activity of ceftaroline. Bactericidal activity was observed by 8–24 hours with all concentrations against 12 of 17 isolates, and with 4 and/or 8 × MIC against an additional three isolates. A reduction of 2 $\log_{10}$ cfu/mL after 24 hours of incubation was noted for the remaining two strains, one PSSP and one PRSP. Sader et al.[45] additionally reported the MIC and MBC values for 72 isolates of *S. pneumoniae*, 61 of which were not susceptible to penicillin. Ceftaroline and ceftriaxone demonstrated MIC/MBC ratios of ≤2 for 90.3% of isolates and ratios of ≤4 for 94.4% of isolates, while four isolates showed high MIC/MBC ratios (≥32) for both cephalosporins. Saravolatz et al.[42] performed MIC/MBC determinations for a collection of genetically characterized resistant isolates of *S. aureus*. Ceftaroline MBC_{90} values were equal to the MIC_{90} values for CA-MRSA (1 mg/L) and VISA/hVISA (1 mg/L) isolates, and against daptomycin-nonsusceptible *S. aureus* and VRSA, the geometric mean MBCs were <2-fold higher than the mean MICs.

In the study by Jones et al.[44] modifying several CLSI broth microdilution test conditions had minimal effects on the reference MIC for ceftaroline. Only 16 MICs among 165 results varied by more than 4-fold when compared with the baseline ceftaroline reference. Use of an acidic medium (pH 5.0) was responsible for 9 of the 16 significant variations; results were markedly lower than baseline MICs, possibly due to either suboptimal growth conditions or instability of

ceftaroline under these conditions.[44] Similar findings of ceftaroline MIC determinations being generally robust to alterations to the CLSI reference test conditions were made by Citron and Goldstein,[46] who also noted the exception of poor growth of *H. influenzae* and *Moraxella catarrhalis* isolates in medium of low pH (pH 6) and (along with *S. pyogenes* and *S. pneumoniae* isolates) in medium with high salt (5% NaCl).

There is evidence of synergism of ceftaroline combined with certain other antibacterials for improved activity against multidrug-resistant Gram-negative pathogens, including ESBL-producing *E. coli* and *K. pneumoniae*, *P. aeruginosa* and AmpC-overexpressed Enterobacteriaceae.[47,48] A broth microdilution checkerboard technique was used to generate fractional inhibitory concentration (FIC) values for combinations of ceftaroline and several antibacterials to investigate both synergistic and antagonistic interactions; FIC index values were interpreted as ≤0.5 for synergism, >0.5–4 for no interaction and >4 for antagonism.[47] Organisms tested included *S. aureus*, *E. faecalis*, *S. pyogenes*, *S. pneumoniae*, *K. pneumoniae*, *E. coli*, *Acinetobacter baumannii*, *P. aeruginosa* and *H. influenzae*. Synergy was detected with a combination of ceftaroline plus meropenem for *S. aureus* 2202 (CA-MRSA) and *K. pneumoniae* 1468 (ESBL-producing strain), and ceftaroline plus amikacin for *E. coli* 2273 (ESBL-producing strain) and *P. aeruginosa* 2559. There was no evidence of antagonism with any of the ceftaroline combinations tested.[47] Vidaillac et al.[48] showed in time-kill studies that the combination of ceftaroline plus amikacin was synergistic against nine of ten tested strains, including *P. aeruginosa*. In time-kill studies, ceftaroline exhibited synergy when combined with amikacin against ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, AmpC-derepressed *E. cloacae* and *P. aeruginosa*; in combination with piperacillin/tazobactam against ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae*; in combination with meropenem against ESBL-producing *E. coli*; and in combination with aztreonam against AmpC-derepressed *E. cloacae*. Synergy was defined as >2 $\log_{10}$ cfu/mL killing compared with the most efficient agent at 24 hours. Vidaillac et al.[49] also observed synergistic effects between ceftaroline and tobramycin against HA-MRSA and hVISA. Additional studies of the synergistic effects of ceftaroline used in combination with other antibacterials are warranted to help address the challenges of emerging resistance and selection of appropriate antibacterial treatment regimens.

5. Pharmacokinetics

5.1 Absorption

The pharmacokinetic parameters for ceftaroline obtained from studies performed in healthy adult volunteers are shown in table III.[50-52] The intravenous and intramuscular dosage forms of ceftaroline have been studied in single-dose and multiple-dose studies.[52] The pharmacokinetics of ceftaroline have also been evaluated in patients with impaired renal function (table IV),[53] and a population pharmacokinetic analysis of these data was performed to establish a population pharmacokinetic database to explore the probability of pharmacokinetic/pharmacodynamic target attainment by simulation.[53,54]

Ceftaroline fosamil is a prodrug that is rapidly converted by plasma phosphases to its bioactive metabolite, ceftaroline. In single-dose studies, ceftaroline has been administered in doses of 50, 100, 250, 500, 750 and 1000 mg as an intravenous infusion over 60 minutes. Maximum plasma concentration (C_{max}), and area under the concentration-time curve (AUC) for the prodrug, ceftaroline and the inactive ceftaroline-M-1 metabolite increased approximately in proportion to dose and were independent of dose duration (table III).[50] In multiple-dose studies in healthy volunteers, after administration of intravenous ceftaroline 300 or 600 mg every 12 hours over a period of 14 days, the C_{max} values following the first dose were 10 and 19 μg/mL, respectively, and 8.4 and 21 μg/mL following the last dose, showing no accumulation over the dose range and populations studied. Similarly, for multiple dosages of 800 mg every 24 hours, C_{max} values for first and last doses were 29.3 and 31.4 μg/mL, respectively.[51]

Table III. Pharmacokinetic parameters of ceftaroline evaluated in healthy volunteers[50-52]

Study	Dosage[a] (mg)	C_{max} (μg/mL)	t_{max} (h) [median]	AUC (h • μg/mL)	$t_{1/2}$ (h)	Vd (L/kg)[b]	CL_R (mL/min)	% Excreted unchanged[c]
Ge et al.[50]	250 IV×1 dose	9.9		22.9	2.31	0.31	73.4	45.7
	500 IV×1 dose	16.5		44.8	2.51	0.38	92.7	56.3
	750 IV×1 dose	23.0		56.9	2.61	0.36	104.9	54.1
	1000 IV×1 dose	30.2		80.5	2.89	0.40	129.2	70.7
Ge et al.[51]	300 IV q12h×14 d	8.4[d]		24.1[d]	2.6[d]	0.45	72.9[d]	39.8[d]
	600 IV q12h×14 d	21		55.7	2.6	0.34	112.3	69
	800 IV q24h×7 d	31.4		72.9	2.6	0.31	63.4	39.3
Riccobene et al.[52]	400 IM×1 dose	6.97	1.5	35.6	2.36		110	
	600 IM×1 dose	8.5	2	48.1	2.55		114	
	1000 IM×1 dose	16	2	110	2.68		90	
	600 IV×1 dose	19.7	0.98	45	2.13		108	
	600 IM q12h day 1	11.6	2	55.3	2.5		110	
	600 IM q12h day 5	13	2	65.4	2.5		95	

a Doses administered as 60-min intravenous infusion.

b Vd calculated by (dose/C_{max})/average weight (kg) of cohort.

c Ceftaroline-M-1 (inactive metabolite) excreted in urine in small amounts.[50,51]

d Value following last dose (14 or 7 d).

AUC = area under the concentration-time curve; **CL_R** = renal clearance; **C_{max}** = maximum plasma concentration; **IM** = intramuscular; **IV** = intravenous; **q*x*h** = every *x* hours; **$t_{1/2}$** = half-life; **t_{max}** = time to reach maximum plasma concentration; **Vd** = volume of distribution.

The pharmacokinetics if ceftaroline following intramuscular administration of single doses of 400, 600 and 1000 mg have been compared with those of 600 mg administered intravenously.[52] The pharmacokinetics have also been evaluated after multiple doses of 600 mg administered intramuscularly every 12 hours for 5 days (table III). The absolute bioavailability of the intramuscular 600 mg dose was 100% of the intravenous dose, indicating that systemic exposure to intramuscular ceftaroline 600 mg was approximately equivalent to ceftaroline 600 mg administered intravenously. The AUC and half-life of the two regimens were similar (table III). There was slight delay in the time to achieve C_{max} with the intramuscular administration compared with that of the intravenous infusion (2 vs 0.98 hours, respectively). This could be accounted for by the slow release of the prodrug from the intramuscular site of injection and limited conversion to active ceftaroline in the intramuscular space. Of note, the mean length of time free-drug serum concentrations exceeded the MIC (%T > MIC) [assuming 20% protein binding] on day 5 following intramuscular ceftaroline fosamil 600 mg every 12 hours for MICs of 0.12–2.0 μg/mL ranged from 99.8% to 65%, suggesting that 600 mg intramuscularly every 12 hours can be expected to be efficacious for micro-organisms with MICs ≤2 μg/mL.

A population analysis using pharmacokinetic data collected from 127 phase I and II study participants (54 healthy, 23 renally impaired, 50 with cSSSIs) suggests that the data fit well into a two-compartment pharmacokinetic model with zero-order input and first-order elimination.[54]

5.2 Distribution

The volume of distribution of ceftaroline (assuming complete conversion of prodrug) is 28.3 L (0.37 L/kg; range 0.31–0.45; table III), representing distribution into the total body water compartment.[53] Bodyweight has a modest effect on volume of distribution for ceftaroline for both central and peripheral compartments.[54] Plasma protein binding of ceftaroline is low (<20%).[55] Currently, tissue penetration data are limited.

Of interest is a study conducted in a rabbit model designed to evaluate the penetration of intravenous ceftaroline into lung tissue compared with the corresponding plasma level. Following a ceftaroline dose of 20 mg/kg, rabbits were sacrificed and the mean penetration rate into the lung was 42.0 ± 11.2% (relative to plasma), suggesting that these penetration rates should allow sufficient time above MIC for the majority of respiratory pathogens.[56]

5.3 Metabolism and Excretion

After conversion of the prodrug ceftaroline fosamil in the plasma to the bioactive metabolite, ceftaroline, a small fraction is converted to an inactive metabolite, ceftaroline-M-1. The half-life of active ceftaroline is 2.6 hours (range 2.3–2.9 hours) and that of ceftaroline-M-1 metabolite is 4.51 hours (±33.1%) in healthy volunteers.[50,51] Drug accumulation does not occur following multiple doses of ceftaroline with dose administration intervals of either 12 or 24 hours for 5–14 days.[51] Ceftaroline and ceftaroline-M-1 are eliminated primarily through renal excretion with average renal clearances for ceftaroline of 95.6 mL/min (single dose) and 86.7 mL/min (multiple doses).[50,51] Approximately half the dose of ceftaroline is excreted in the urine as active drug (average 49.6%), with a small amount excreted in the urine as ceftaroline-M-1 (average 7.4%). No prodrug was reported to be excreted in urine.[50,51,53]

The pharmacokinetics of ceftaroline have been studied in patients with mild renal impairment (creatinine clearance [CL_{CR}] 50–80 mL/min) and moderate renal impairment (CL_{CR} 30–50 mL/min).[53] In this study,[53] 18 subjects were divided into three cohorts (six per group) based on renal function; normal renal function (CL_{CR} >80 mL/min), mild impairment or moderate impairment. Following a single intravenous dose of ceftaroline 600 mg, pharmacokinetic parameters were assessed (table IV). The C_{max} and time to reach maximum concentration did not differ between groups. In contrast, plasma half-life increased from 2.84 hours in those with normal renal function to 3.61 hours in those with mild and 4.49 hours in those with moderate renal impairment. Consistent with the increase in plasma half-life, the AUC was also significantly larger for the moderate renal impairment group (114 vs 35.6 μg • h/mL in normal renal function group) and renal clearance declined from normal renal function (54.6 mL/min) to mild (30.8 mL/min) to moderate (19.3 mL/min) impairment (table IV). Renal impairment also had a significant effect on the pharmacokinetics of ceftaroline-M-1. The C_{max}, AUC and half-life of ceftaroline-M-1 increased significantly in moderate renal impairment, and the renal clearance decreased by 55% and 84% in subjects with mild and moderate renal impairment, respectively.[53] Based on these findings, dosage adjustment is needed in patients with moderate but not mild renal impairment. Using a population pharmacokinetic model, MIC data from clinically relevant organisms and pharmacokinetic/pharmacodynamic targets from nonclinical animal infection models, Monte Carlo simulations were conducted to estimate the probability of pharmacokinetic/pharmacodynamic target attainment. In patients with normal kidney function or mild renal impairment, the recommended dose is 600 mg intravenously infused over 1 hour every 12 hours and the suggested dosage adjustment for patients with moderate renal impairment (30–50 mL/min) is 400 mg intravenously infused over 1 hour every 12 hours.[57]

Table IV. Pharmacokinetics of a single intravenous ceftaroline 600 mg dose in subjects with renal impairment[53]

Renal status (CL_{CR} mL/min)	C_{max} (μg/mL)	t_{max} (h)	AUC (μg • h/mL)	$t_{1/2}$ (h)	CL_R (mL/min)	% Dose in urine
Normal (CL_{CR} >80)	27.6	0.97	35.6	2.84	54.6	46.4
Mild (CL_{CR} >50–80)	27.7	0.99	89.4	3.61	30.8	31.2
Moderate (CL_{CR} >30–50)	30.5	1.1	114	4.49	19.3	24.9

AUC = area under the concentration-time curve; **CL_{CR}** = creatinine clearance; **CL_R** = renal clearance; **C_{max}** = maximum plasma concentration; **IV** = intravenous; **t_{max}** = time to maximum plasma concentration; **$t_{1/2}$** = half-life.

6. Pharmacodynamics

The pharmacodynamics of ceftaroline have been evaluated in a number of studies. The antibacterial efficacy of β-lactams is best measured by %T > MIC. A bacteriostatic effect was achieved when free drug concentrations exceeded the MIC for 30% (30% T > MIC) of the dose administration interval for staphylococci and for 40% (40% T > MIC) of the dose administration interval for Gram-negative bacilli. Near maximum organism kill (bactericidal activity) is achieved at 50% and 60% T > MIC for staphylococci and Gram-negative bacilli, respectively.[58-60]

Andes and Craig[58] studied the pharmacodynamics of ceftaroline in neutropenic mouse thigh and lung infection models, and confirmed that %T > MIC is the best pharmacokinetic/pharmacodynamic predictor of efficacy for ceftaroline. They also determined the magnitude of the pharmacokinetic/pharmacodynamic index associated with efficacy. Mice were infected with *S. pneumoniae* (six strains), *S. aureus* (three strains), *E. coli* (two strains) or *K. pneumoniae* (three strains). Single doses of ceftaroline (1.56, 6.25, 25, 100 mg/kg of bodyweight) were administered and the treated groups were sampled nine times over a 24-hour period. Free-drug %T > MIC associated with a bacteriostatic effect as well as 1 and 2 log killing were calculated for each organism. Mean %T > MIC (± SD) for *S. pneumoniae*, *S. aureus* and Gram-negative bacilli to produce a bacteriostatic effect were 39 ± 9%, 26 ± 8% and 28 ± 9%, respectively. For 1 and 2 log killing, %T > MIC for *S. pneumoniae*, *S. aureus* and Gram-negative bacilli were as follows: 43 ± 9%, 33 ± 9% and 41 ± 11% (1 log) and 50 ± 10%, 45 ± 13% and 54 ± 3% (2 log), respectively. The free-drug %T > MIC necessary for efficacy was slightly reduced for animals with normal neutrophil counts.[17,58]

7. Animal Studies

Animal studies evaluating ceftaroline against numerous pathogens have demonstrated clinical efficacy in systemic, lung and thigh infections; endocarditis; and osteomyelitis models (table V).[30,61-65]

In a series of experiments conducted by Iizawa et al.[30] in mice, the effect of ceftaroline was evaluated in systemic, lung and thigh infections caused by clinical isolates of MRSA. In the systemic infection model, four clinical isolates of MRSA (TY5826, TY6007, TY5993 and TY6242) were used; MIC values for the four MRSA isolates ranged from 0.5 to 2.0 mg/L for ceftaroline, from 0.5 to 1.0 mg/L for vancomycin and 2.0 mg/L for linezolid. Two experiments were conducted to determine the protective efficacy of ceftaroline treatment relative to comparators in a mouse systemic infection model: one was a comparative study with vancomycin, teicoplanin and arbekacin, and the other was a comparison with linezolid. Varying doses of drugs were administered subcutaneously 1 hour after bacterial challenge, and groups of ten mice were used for each treatment. Ceftaroline was equal to or more effective than the comparator agents against the four strains of MRSA tested (median effective dose for ceftaroline: [TY5826] 1.08 mg/kg; [TY6007] 1.46 mg/kg; [TY5993] 4.81 mg/kg; [TY6242] 2.09 mg/kg). The pneumonia model evaluated the efficacy of ceftaroline compared with vancomycin and linezolid against MRSA (TY6001). In two experiments, drugs were administered 2 hours, 1 day and 2 days after infection; a dose of 20 mg/kg/administration was used for all drugs and ten mice were included in each treatment group. When treatment was started 2 hours after infection, all three agents showed equal efficacy. When treatment was started 1 day after infection, ceftaroline decreased bacterial cell counts in lung tissue by >99.9%, whereas vancomycin and linezolid did not affect bacterial counts. In the thigh infection study, MRSA (N133) was injected in the left thigh muscle of mice. Ceftaroline, vancomycin or linezolid at a dose of 20 mg/kg/administration was administered subcutaneously 2, 20 and 26 hours after infection. Treatment with ceftaroline and linezolid decreased bacterial counts in muscle to ≤0.1%; the activity of vancomycin was less than that of ceftaroline and linezolid. These results demonstrate that ceftaroline is an effective anti-MRSA agent *in vivo*.

Table V. Animal studies involving ceftaroline (CPT)

Study	Animal model	Dosage	Duration (d)	Number of animals	Results (log_{10} cfu/g)
Xiong et al.[63]	Rat *Staphylococcus aureus* endocarditis model	Control	3	12	Heart tissue: 9.87 ± 0.49
		CPT 20 mg/kg IV bid		9	4.88 ± 0.57
		VAN 120 mg/kg SC bid		7	6.76 ± 0.98
		DAP 10 mg/kg SC od		6	7.64 ± 0.32
Jacqueline et al.[61]	Rabbit MRSA endocarditis model	**MRSA**			
		Control	4	6	Cardiac vegetations: 8.9 ± 0.5
		CPT 10 mg/kg q12h		10	2.5 ± 0.3
		VAN continuous infusion (Css 20× MIC)		6	2.7 ± 0.8
		LZD 10 mg/kg q12h		7	7.1 ± 0.6
		hGISA			
		Control		6	Cardiac vegetations: 9.4 ± 0.3
		CPT 10 mg/kg q12h		10	3.0 ± 0.9
		VAN continuous infusion (Css 20× MIC)		5	6.7 ± 0.4
		LZD 10 mg/kg q12h		8	6.9 ± 0.4
Jacqueline et al.[64]	Rabbit MRSA endocarditis model	Control	4	10	Cardiac vegetations: 8.99 ± 0.47
		CPT 40 mg/kg IM bid		10	2.45 ± 0.14
		CPT 20 mg/kg IM bid		10	3.14 ± 1.38
		CPT 5 mg/kg IM bid		9	5.26 ± 2.73
		TEC 20 mg/kg IM bid		10	3.07 ± 0.66
Jacqueline et al.[65]	Rabbit *Enterococcus faecalis* endocarditis model	**EF 12704 (Van-sensitive)**			
		Control	4	8	Cardiac vegetations: 8.56 ± 0.74
		CPT 10 mg/kg q12h		7	5.68 ± 0.49
		LZD 10 mg/kg q12h		7	6.88 ± 0.70
		VAN continuous infusion (Css 20× MIC)		8	6.70 ± 0.25
		EF NJ1 (Van-resistant)			
		Control		9	Cardiac vegetations: 8.60 ± 0.54
		CPT 10 mg/kg q12h		9	3.98 ± 0.85
		LZD 10 mg/kg q12h		7	6.88 ± 0.77
		VAN continuous infusion (Css 20× MIC)		8	6.70 ± 0.25
Jacqueline et al.[62]	Rabbit MRSA and GISA osteomyelitis experimental model	**MRSA strain**			
		Control	4	8	Mean Δ (JF) 0.09 ± 0.59 (BM) 0.20 ± 0.59 (BO) 0.11 ± 0.81

Continued next page

Table V. Contd

Study	Animal model	Dosage	Duration (d)	Number of animals	Results (log_{10} cfu/g)
		CPT 10 mg/kg q12h		10	Mean Δ (JF) −1.98 ± 1.00 (BM) −2.95 ± 0.44 (BO) −2.83 ± 1.50
		VAN continuous infusion (Css 20× MIC)		10	Mean Δ (JF) −0.19 ± 1.19(BM) −0.39 ± 1.60 (BO) −0.52 ± 0.69
		LZD 10 mg/kg q12h		8	Mean Δ (JF) −0.77 ± 1.39 (BM) −2.69 ± 1.92 (BO) −2.25 ± 1.55
Jacqueline et al.[62]	Rabbit MRSA and GISA osteomyelitis experimental model	**GISA strain**			
		Control	4	8	Mean Δ (JF) 0.86 ± 0.30 (BM) 0.63 ± 0.57 (BO) 0.23 ± 0.41
		CPT 10 mg/kg q12h		8	Mean Δ (JF) −1.55 ± 0.52 (BM) −2.02 ± 0.93 (BO) −2.01 ± 0.90
		VAN continuous infusion (Css 20× MIC)		8	Mean Δ (JF) −0.68 ± 0.37 (BM) −0.41 ± 0.43 (BO) −0.57 ± 0.47
		LZD 10 mg/kg q12h		8	Mean Δ (JF) −1.10 ± 1.15 (BM) −2.38 ± 1.02 (BO) −2.23 ± 1.08

bid = twice daily; **BM** = bone marrow; **BO** = bone; **Css** = steady-state; **DAP** = daptomycin; **GISA** = glycopeptide-intermediate *S. aureus*; **hGISA** = heterogeneous glycopeptide-intermediate *S. aureus*; **IM** = intramuscular; **IV** = intravenous injection; **JF** = joint fluid; **LZD** = linezolid; **MIC** = minimum inhibitory concentration; **MRSA** = meticillin-resistant *S. aureus*; **od** = once daily; **q12h** = every 12 hours; **SC** = subcutaneous injection; **TEC** = teicoplanin; **VAN** = vancomycin.

Xiong et al.[63] conducted a study using a rat endocarditis model to test the therapeutic efficacy of ceftaroline versus vancomycin or daptomycin. An indwelling ventricular catheter was placed into each rat, and 1 week later the animals were infected with ~10^5 cfu of *S. aureus* Xen29, a bioluminescent strain of MSSA that allowed detection by an *in vitro* imaging system by bioluminescence signals. These signals were then used to quantify the growth or decline of the *S. aureus*. Approximately 16 animals were allocated to each treatment group, with half the animals in the efficacy group and half in the relapse (no further therapy after the first 3 days) group. Twenty-four hours post-infection, the rats received either no treatment (controls) or a 3-day course of ceftaroline, vancomycin or daptomycin. Twenty-four hours after the last antibacterial dose, half the animals were euthanized and their heart, spleen and kidneys were analyzed for microbial growth while the other half went on to relapse testing (no additional therapy) after an additional 3 days. Ceftaroline- and vancomycin-treated rats showed a significant decline in cfu values in heart vegetations as compared with the control group (table V). *S. aureus* counts in heart tissue for controls, ceftaroline, vancomycin and daptomycin groups were 9.87 ± 0.49, 4.88 ± 0.57, 6.76 ± 0.98 and 7.64 ± 0.32 log_{10} cfu/g, respectively, indicating that ceftaroline penetrated well into the site of infection in this endocarditis model. There was a trend towards relapse prevention in the ceftaroline-treated rats, although the differences were not statistically significant.

Jacqueline et al.[61] compared the *in vivo* efficacy of simulated human dosing of ceftaroline with vancomycin and linezolid against MRSA in a rabbit endocarditis model. One MRSA and one hGISA strain were studied, with inocula of 10^8 cfu of each organism to initiate endocarditis. To determine the kinetics for ceftaroline, six healthy rabbits were administered a ceftaroline bolus dose of 10 and 30 mg/kg. The results were then compared with human kinetics, and a dose of 58 mg/kg infused using a computer-controlled pump over a 12-hour period for the rabbits was determined to reflect a human dose of 600 mg infused over 1 hour every 12 hours. For both the

MRSA and hGISA strains, animals were randomized to one of four groups; controls (no treatment), ceftaroline, linezolid or vancomycin. Treatment duration was 4 days. Ceftaroline demonstrated excellent bactericidal activity against both the MRSA and hGISA strains after a 4-day treatment, whereas vancomycin and linezolid achieved only bacteriostatic activity against hGISA. Table V shows values for bacterial titres in vegetations after 4 days of treatment. Ceftaroline yielded the lowest counts in the vegetations for both the MRSA and hGISA strains (2.5 ± 0.3 and 3.0 ± 0.9 $\log_{10}$ cfu/g, respectively). Sterilization rates were also recorded for each antibacterial to compare efficacy. A vegetation was considered sterile if no bacterial growth was detected after 48 hours of incubation at 37°C. For MRSA and hGISA, respectively, ceftaroline achieved sterilization rates of 90% and 60%, whereas vancomycin achieved 67% and 0%. Linezolid did not achieve sterilization for either strain. Compared with vancomycin and linezolid, ceftaroline was the most effective antibacterial for treating hGISA in this model, demonstrating its potential role in severe MRSA infections.[61]

The efficacy of intramuscular administration of ceftaroline against MRSA was also evaluated using the rabbit endocarditis model.[64] Experimental endocarditis was induced with a MRSA strain with heterogeneous high-level meticillin resistance (MIC = 128 mg/L). Animals (10 per group) were randomly assigned to 4 days of no treatment (control), intramuscular ceftaroline at three dosages (see table V) or intramuscular teicoplanin, all administered 24 hours after inoculation. Bacterial titres in vegetations after 4 days of treatment are shown in table V. The efficacy of intramuscular ceftaroline was similar to that achieved with intravenous ceftaroline in the previously mentioned study[61] (table V). After 4 days of treatment, intramuscular ceftaroline at doses of 20 and 40 mg/kg twice daily demonstrated excellent bactericidal activity against MRSA, suggesting that intramuscular ceftaroline may also be an effective therapeutic option for treatment of severe MRSA infections.

The *in vivo* activity of ceftaroline was compared with control, linezolid and vancomycin against two *E. faecalis* strains (EF 12704 [vancomycin-susceptible] and EF NJ1 [vancomycin-resistant]) using simulated human therapeutic doses in a rabbit endocarditis model.[65] MICs for EF 12704 and EF NJ1 strains were 2 and 1 mg/L for ceftaroline, 2 and >256 mg/L for vancomycin, and 2 and 1 mg/L for linezolid, respectively. Linezolid displayed nonbactericidal, time-dependent activity *in vitro* on enterococci. Vancomycin displayed only poor activity against both EF strains, despite the susceptibility of the EF 12704 strain to vancomycin. Bactericidal and time-dependent activity was observed for ceftaroline at 24 hours against EF 12704 and EF NJ1. Bacterial titres in vegetations after 4 days of treatment are shown in table V; ceftaroline had the lowest counts for both vancomycin-susceptible and -resistant strains of *E. faecalis* (5.68 ± 0.49 and 3.98 ± 0.85 $\log_{10}$ cfu/g, respectively). Thus, the considerable activity of ceftaroline against *E. faecalis* suggests that this new cephalosporin is a reasonable therapeutic option for patients who would be candidates for vancomycin or linezolid treatment.

In another animal study, Jacqueline et al.[62] compared the efficacy of simulated human dosing of ceftaroline against vancomycin and linezolid in a MRSA and GISA rabbit osteomyelitis model. For both MRSA and GISA, 10^9 cfus were inoculated into the knee joint of each rabbit and after 3 days bacterial loads were determined through surgical debridement and lavage. A 4-day treatment of ceftaroline, linezolid or vancomycin was administered to the rabbits, with doses set to mimic human drug concentrations. After antibacterial treatment, bacterial loads were recorded in joint fluid, bone marrow and bone, and compared with the counts on day 3 post-infection. Ceftaroline demonstrated significant activity against both MRSA and GISA for all three infected tissues and was significantly more effective than vancomycin (table V). Although linezolid showed good activity against MRSA and GISA, only ceftaroline was effective in joint fluid infected by MRSA. The researchers concluded that ceftaroline is a promising therapeutic option for safe and effective treatment of infections involving MRSA, and has a spectrum of activity

that includes common pathogens responsible for orthopaedic infections.

8. Clinical Trials

Talbot et al.[11] performed a safety and efficacy study of ceftaroline compared with vancomycin and aztreonam in patients with cSSSI. This phase II, multicentre, randomized (2 : 1), observer-blinded study compared a regimen of intravenous ceftaroline 600 mg every 12 hours with a standard therapy group that consisted of intravenous vancomycin 1 g every 12 hours initially (table VI).[11,15] Both ceftaroline and standard therapies were administered for 7–14 days. 100 patients were initially enrolled in the study. At the end of the study, 61 patients were clinically evaluable for ceftaroline and 27 for standard therapy (total of 88 clinically evaluable), and 96.7% of patients were clinically cured with ceftaroline compared with 88.9% of those treated with standard therapy. In the microbiologically evaluable population, the microbiological success rate was 95.2% (40/42) for ceftaroline and 85.7% (18/21) for the standard therapy group (table VI). Of the five patients from each treatment group who were confirmed to have MRSA infections, four of five patients treated with ceftaroline and five of five patients treated with standard therapy achieved clinical cures. The most common adverse events in both treatment groups included the presence of urinary crystals, increased creatine phosphokinase (unaccompanied by muscle or cardiac symptoms), headache and insomnia. Adverse events between both treatment groups were similar, with 61.2% of patients in the ceftaroline group and 56.3% of patients in the standard therapy group reporting an event.[11]

Phase III clinical trials (CANVAS I and II) in cSSSI have been completed by Forest Laboratories, Inc.[66] CANVAS I evaluated the efficacy and safety of ceftaroline compared with vancomycin plus aztreonam in patients with cSSSI. A total of 702 patients with local and systemic evidence of cSSSI were randomized to either intravenous ceftaroline 600 mg or vancomycin 1 g plus aztreonam 1 g, each administered every 12 hours for 5–14 days (aztreonam was discontinued if a Gram-negative pathogen was not identified or suspected).[15] Disease severity was similar between groups; deep/extensive cellulitis and major abscess were the most common types of infections and *S. aureus* was the most common organism isolated. Surgical procedures were performed in 9.1% of ceftaroline-treated patients and 6.9% of vancomycin plus aztreonam-treated patients. Of the microbiologically evaluable patients treated with ceftaroline (n = 244)

Table VI. Clinical trials of ceftaroline in complicated skin and skin-structure infections

Trial	Number of patients	Dosage regimen (no. treated)	Microbiological response	Clinical response	Reference
Phase II, randomized, comparative	100 (88 clinically evaluable)	Ceftaroline: IV 600 mg q12h for 7–14 d (67) Standard therapy: vancomycin IV 1 g q12h initially; if baseline cultures indicated a Gram-positive organism susceptible to PRP, therapy switched to a PRP within 72 h of start of therapy. If cultures indicated a Gram-negative organism, concomitant aztreonam 1 g q8h was given (32). Duration: 7–14 d	Ceftaroline: 95.2% eradication rate Standard therapy: 85.7% eradication rate	Ceftaroline: 96.7% clinically cured Standard therapy: 88.9% clinically cured	11
CANVAS I (phase III, randomized, comparative)	702	Ceftaroline: IV 600 mg q12h (351) Vancomycin: IV 1 g + aztreonam IV 1 g q12h (347). Duration: 5–14 d	Ceftaroline: 94.9% eradication rate (MRSA only) Vancomycin + aztreonam: 91.8% eradication rate (MRSA only)	Ceftaroline: 94.9% clinically cured (MRSA only) Vancomycin + aztreonam: 95.1% clinically cured (MRSA only)	15

IV = intravenous; **MRSA** = meticillin-resistant *Staphylococcus aureus*; **PRP** = penicillinase-resistant penicillin; **q***x***h** = every *x* hours.

compared with those treated with vancomycin plus aztreonam (n = 227), clinical cure rates were 94.9% and 95.1% for MRSA; 100% for both groups for *S. pyogenes*; 92.9% and 100% for *S. agalactiae*; 92.9% and 91.7% for *E. faecalis*; 90% and 86.7% for *E. coli*; and 100% and 90% for *P. aeruginosa*, respectively.[15] The high response rate in this trial for ceftaroline against *P. aeruginosa*, a species against which ceftaroline has limited activity *in vitro*, may reflect the polymicrobial nature of these *Pseudomonas* infections. In a polymicrobial infection, the determination of pathogen status is complicated, and *Pseudomonas* isolates from polymicrobial cSSSI such as those studied in this trial are more likely to be colonizing bacteria rather than active pathogens. Microbiological eradication rates for ceftaroline and vancomycin plus aztreonam were 94.9% and 91.8% for MRSA; 100% for both groups for *S. pyogenes*; 85.7% and 100% for *S. agalactiae*; 92.9% and 91.7% for *E. faecalis*; 90% and 86.7% for *E. coli*; and 88.9% and 90% for *P. aeruginosa*, respectively (table VI). Ceftaroline was proven to be non-inferior to the standard therapy of vancomycin plus aztreonam in treating patients with cSSSI caused by both Gram-positive and Gram-negative pathogens. The study showed that ceftaroline was well tolerated with adverse event rates similar between both treatment groups. The most common adverse event was nausea (5.7%) in the ceftaroline group and pruritus (8.4%) in the vancomycin plus aztreonam group. Results from CANVAS II are currently undergoing analysis.

9. Adverse Effects/Drug Interactions

Although the adverse effect profile of ceftaroline is still being established, current data from clinical studies show that ceftaroline is well tolerated. Phase I studies reported no serious or life-threatening adverse effects, no dose-limiting toxicities, and no clinically significant changes in biochemistry, haematology, coagulation or urinalysis.[50,51,53] In the phase II study, 61.2% of the ceftaroline treatment group and 56.3% of the standard therapy (vancomycin plus aztreonam) group experienced adverse effects.[11] The majority (87.9%) of adverse effects reported in the ceftaroline group were mild compared with 70.8% in the standard therapy group. The 1-hour infusion of ceftaroline was well tolerated; two patients reported injection-site pain, one reported swelling and one reported site bruising (thrombosis). In addition, ECG data suggested no QT interval prolongation for ceftaroline.[11] Analysis of a larger, more representative sample assessing adverse events was recently conducted. Data from CANVAS I indicated that the percentage of patients experiencing an adverse event was similar for ceftaroline compared with the vancomycin plus aztreonam treatment group; most adverse events were mild and judged not related to treatment.[15] Nausea (5.7%) was the most common adverse event in the ceftaroline group and pruritus (8.4%) was most common in the vancomycin plus aztreonam group. Generally, ceftaroline is well tolerated, consistent with the good safety and tolerability profile of the cephalosporin class.

Little information on the potential of ceftaroline for drug-drug interactions is currently available. Ge and Hubbel[55] found that ceftaroline demonstrated little interaction with human liver microsomes. Considering that the primary route of elimination of ceftaroline and its metabolites is renal, drug-interaction potential involving the cytochrome P450 system is likely to be low.[55]

10. Role of Ceftaroline in Therapy

Ceftaroline has demonstrated good activity against a wide spectrum of pathogens, including Gram-positive cocci, MRSA, meticillin-resistant *S. epidermidis*, PRSP and *E. faecalis*, and possesses comparable activity to third-generation cephalosporins, such as ceftazidime and ceftriaxone, against most Gram-negative pathogens. Ceftaroline holds promise for empirical treatment of infections in place of complex multiple antibacterial regimens in emergency departments. Ceftaroline is particularly promising for the treatment of CA-MRSA, and has the advantages of both a better adverse-effect profile and superior bactericidal activity compared with both

vancomycin and linezolid. In addition, and as evidenced by its strong activity against *Staphylococcus* and *Streptococcus* spp., including those resistant to conventional β-lactams in use today, ceftaroline may be used as empirical monotherapy in place of complex combination therapies. Ceftaroline has proven to be efficacious in the treatment of cSSSI (clinical trials) and has also been found to be efficacious in the treatment of MRSA and GISA osteomyelitis and endocarditis in rabbits. In addition, preliminary safety data look promising for ceftaroline, with the majority of reported adverse effects mild in nature. Patients who are intolerant or have not responded to other antibacterial therapies may benefit from this promising alternative.

11. Potential Future Developments for Ceftaroline

The race against antibacterial resistance is a constant one, requiring new and innovative antibacterials. ESBL-producing bacteria are of particular concern because of the emergence of multi-resistant isolates. Alternative strategies aimed at different targets are being considered to combat the overwhelming threat of bacterial resistance. Currently, an investigational non-β-lactam β-lactamase inhibitor, NXL 104, has been developed and tested with cephalosporin combinations in an attempt to restore activity against ESBL-producing Enterobacteriaceae.[67-69] In January 2008, Forest Laboratories, Inc. and Novexel (developer of NXL 104) announced a collaboration to begin phase I clinical trials with the combination ceftaroline/NXL 104 in the next year.[70] Ceftazidime/NXL 104 is also being evaluated by Novexel in phase II clinical trials in hospitalized patients with complicated urinary tract infections.[71] These unique drug combinations may play an important role in the future of antibacterial therapy. Because bacteria are constantly developing resistance to antibacterials, further exploration of new targets, novel chemical classes and unique mechanisms to inhibit resistance is likely to expand the pipeline for new antibacterial agents.

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