CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will understand ceftaroline's place in therapy and optimize its use

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Ceftaroline fosamil: A super-cephalosporin?

ABSTRACT

Ceftaroline is a broad-spectrum cephalosporin used to treat infections caused by a variety of microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae*. However, it is not active against *Pseudomonas aeruginosa, Bacteroides fragilis*, and carbapenem-resistant Enterobacteriaceae. Its approved indications include community-acquired bacterial pneumonia and bacterial infections of skin and skin structures. It has also been used off-label to treat osteomyelitis, endocarditis, and meningitis caused by ceftaroline-susceptible organisms.

KEY POINTS

Resistance of *S aureus* and *S pneumoniae* to multiple antimicrobial drugs is on the rise, and new agents are urgently needed.

Ceftaroline's molecular structure was designed to provide enhanced activity against MRSA and multidrug-resistant *S pneumoniae.*

In clinical trials leading to its approval, ceftaroline was found to be at least as effective as ceftriaxone in treating community-acquired pneumonia and at least as effective as vancomycin plus aztreonam in treating acute bacterial skin and skin-structure infections.

The routine use of ceftaroline for these indications should be balanced by its higher cost compared with ceftriaxone or vancomycin. Ongoing studies should shed more light on its role in treatment.

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Ceftaroline fosamil (Teflaro), introduced to the US market in October 2010, is the first beta-lactam agent with clinically useful activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Currently, it is approved by the US Food and Drug Administration (FDA) to treat acute bacterial skin and skin-structure infections and community-acquired bacterial pneumonia caused by susceptible microorganisms.

In an era of increasing drug resistance and limited numbers of antimicrobials in the drug-production pipeline, ceftaroline is a step forward in fulfilling the Infectious Diseases Society of America's "10 × '20 Initiative" to increase support for drug research and manufacturing, with the goal of producing 10 new antimicrobial drugs by the year 2020.[1] Ceftaroline was the first of several antibiotics to receive FDA approval in response to this initiative. It was followed by dalbavancin (May 2014), tedizolid phosphate (June 2014), oritavancin (August 2014), ceftolozane-tazobactam (December 2014), and ceftazidime-avibactam (February 2015). These antibiotic agents are aimed at treating infections caused by drug-resistant gram-positive and gram-negative microorganisms. It is important to understand and optimize the use of these new antibiotic agents in order to decrease the risk of emerging antibiotic resistance and superinfections (eg, *Clostridium difficile* infection) caused by antibiotic overuse or misuse.

This article provides an overview of ceftaroline's mechanisms of action and resistance, spectrum of activity, pharmacokinetic properties, adverse effects, and current place in therapy.

AN ERA OF MULTIDRUG-RESISTANT MICROORGANISMS

Increasing rates of antimicrobial resistance threaten the efficacy of antimicrobial drugs in the daily practice of medicine. The World Health Organization has labeled antimicrobial resistance one of the three greatest threats to human health. Global efforts are under way to stimulate development of new antimicrobial agents and to decrease rates of antimicrobial resistance.

Staphylococcus aureus: A threat, even with vancomycin

Between 1998 and 2005, *S aureus* was one of the most common inpatient and outpatient isolates reported by clinical laboratories throughout the United States.[2]

Treatment of *S aureus* infection is complicated by a variety of resistance mechanisms that have evolved over time. In fact, the first resistant isolate of *S aureus* emerged not long after penicillin's debut into clinical practice, and now the majority of strains are resistant to penicillin.

Methicillin was designed to overcome this beta-lactamase resistance and became the treatment of choice for penicillin-resistant *S aureus* isolates. However, MRSA isolates soon emerged because of the organism's acquisition of penicillin-binding protein PBP2a via the *mecA* gene, leading to decreased binding affinity of methicillin.[3]

Resistance threatens the efficacy of antimicrobial drugs in the daily practice of medicine

Since then, several agents active against MRSA (vancomycin, daptomycin, linezolid, tigecycline) have been introduced and continue to be widely used. While vancomycin is considered the first-line option for a variety of MRSA infections, its use has been threatened because of the emergence of vancomycin-intermediate-resistant *S aureus* (VISA), *S aureus* strains displaying vancomycin heteroresistance (hVISA), and vancomycin-resistant *S aureus* (VRSA) strains.[4]

VISA and hVISA isolates emerged through sequential mutations that lead to autolytic activity and cell-wall thickening. In contrast, the mechanism of resistance in VRSA is by acquisition of the *vanA* resistance gene, which alters the binding site of vancomycin from D-alanine-D-alanine to D-alanine-D-lactate.[5]

Streptococcus pneumoniae resistance: A continuing problem

The prevalence of drug resistance in *S pneumoniae* has risen since the late 1990s. A 2013 report from the SENTRY Antimicrobial Surveillance Program stated that almost 20% of *S pneumoniae* isolates were resistant to amoxicillin-clavulanate, and similar trends have been observed for penicillin (14.8%) and ceftriaxone (11.7%).[6]

S pneumoniae resistance is acquired through modifications of the penicillin-binding proteins, namely PBP1a, PBP2b, PBP2x, and, less frequently, PBP2a. These modifications lead to decreased binding affinity for most beta-lactams.[7]

Clinical impact of multidrug-resistant *S aureus* and *S pneumoniae*

In 2011, the US Centers for Disease Control and Prevention reported an estimated 80,000 severe MRSA infections and 11,000 MRSA-related deaths in the United States.[8] In the same report, drug-resistant *S pneumoniae* was estimated to be responsible for almost 1.2 million illnesses and 7,000 deaths per year, leading to upwards of $96 million in related medical costs.

While invasive drug-resistant *S pneumoniae* infections usually affect patients at the extremes of age (under age 5 and over age 65), they have had a serious impact on patients of all ages.[8]

In light of the increasing prevalence of multidrug-resistant organisms, newer antimicrobial agents with novel mechanisms of action are needed.

CEFTAROLINE: A BETA-LACTAM WITH ANTI-MRSA ACTIVITY

The cephalosporins, a class of beta-lactam antibiotics, were originally derived from the fungus *Cephalosporium* (now called *Acremonium*). There are now many agents in this class, each containing a nucleus consisting of a beta-lactam ring fused to a six-member dihydrothiazine ring, and two side chains that can be modified to affect antibacterial activity and pharmacokinetic properties.

Cephalosporins are typically categorized into "generations." With some exceptions, the first- and second-generation agents have good

TABLE 1

Antimicrobial activity of ceftaroline fosamil

Organism	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Range
Staphylococcus aureus			
Methicillin-sensitive	0.25	0.25	≤ 0.03–1
Methicillin-resistant	0.5	1.0	0.12–2
Vancomycin-intermediate	0.5	1.0	0.25–1
Daptomycin-nonsusceptible	0.5	0.55	0.25–1
Coagulase-negative staphylococci			
Oxacillin-susceptible	0.06	0.12	≤ 0.03–0.5
Oxacillin-resistant	0.5	0.5	0.06–2
Streptococcus pneumoniae			
Penicillin-sensitive	≤ 0.008	0.015	≤ 0.008–0.12
Penicillin-intermediate	0.015	0.06	≤ 0.008–0.5
Penicillin-resistant	0.12	0.12	≤ 0.008–0.5
Enterobacteriaceae			
Ceftazidime-susceptible	0.06	1.0	≤ 0.03– >16
Ceftazidime-resistant	> 16	>16	0.12– >16

MIC_{50} = the minimum concentration that will inhibit the growth of 50% of organisms
MIC_{90} = the minimum concentration that will inhibit the growth of 90% of organisms

Information from references 10–13.

activity against gram-positive microorganisms, including methicillin-susceptible *S aureus*—but not against MRSA. The third- and fourth-generation cephalosporins have better gram-negative activity, with many agents having activity against the gram-negative bacterium *Pseudomonas aeruginosa*.

Enterococcal isolates are intrinsically resistant to cephalosporins. Additionally, cephalosporins are not active against anaerobic bacteria, except for a subset of structurally unique second-generation cephalosporins, ie, cefotetan and cefoxitin.

Ceftaroline was synthesized with specific manipulations of the side chains to provide enhanced activity against MRSA and multidrug-resistant *S pneumoniae* isolates, making it the first available beta-lactam with this ability.

Mechanism of action

Ceftaroline binds to penicillin-binding proteins, inhibiting transpeptidation. This interaction blocks the final stage of peptidoglycan synthesis and inhibits bacterial cell wall formation, ultimately leading to cellular autolysis and microorganism death. Ceftaroline binds with high affinity to PBP2a and PBP2x, expanding its activity to encompass MRSA and penicillin-resistant *S pneumoniae* isolates.[9]

Methicillin was designed to overcome beta-lactamase resistance in *S aureus*, but MRSA quickly emerged

Spectrum of activity

Ceftaroline has in vitro activity against many gram-positive and gram-negative bacteria,[10–13] including (**Table 1**):

- Methicillin-susceptible and methicillin-resistant staphylococci
- VISA, VRSA, and hVISA
- Daptomycin-nonsusceptible *S aureus*
- Streptococcal species, including penicillin-resistant *S pneumoniae*
- Enterobacteriaceae, including *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Escherichia coli*, *Citrobacter koseri*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Moraxella catarrhalis*, *Morganella morganii*, and *Proteus mirabilis*.

Of note, ceftaroline is not active against *Pseudomonas* species, *Enterococcus* species, or *Bacteroides fragilis*. In addition, it is not active against the "atypical" respiratory pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*.

TABLE 2

Pharmacokinetic profile of ceftaroline fosamil

Maximum concentration: 27.94 ± 4.34 µg/mL[a]

Time to maximum plasma concentration: 1 hour

Volume of distribution: 20.3 L

Protein binding: 20%

Metabolism: No hepatic metabolism; rapidly converted to active drug, ceftaroline, by plasma phosphatase enzymes

Half-life: 2.6 hours

Excretion: 88% renal, 6% fecal

[a] After a 600-mg dose (multiple dose and single dose).

Information from references 16 and 17.

Ceftaroline resistance

Gram-negative organisms appear to develop resistance to ceftaroline at rates similar to those observed with the other oxyimino-cephalosporins (eg, ceftriaxone). Ceftaroline is inactive against gram-negative organisms producing extended-spectrum beta-lactamases, including *K pneumoniae* carbapenemase and metallo-beta-lactamases.[14] In addition, it induces the expression of AmpC beta-lactamases.

Although currently uncommon, resistance to ceftaroline has also been reported in *S aureus* strains.[15] The mechanism of resistance is decreased binding affinity for PBP2a due to amino acid substitutions on the nonpenicillin-binding domains.[15]

Ceftaroline fosamil is typically given in 600-mg IV doses every 12 hours

Pharmacokinetic profile

An understanding of pharmacokinetics is key in optimizing the dose of antimicrobials so that the drugs are used most effectively and pathogens do not develop resistance to them.

Ceftaroline fosamil is a prodrug that, upon intravenous administration, is rapidly converted by phosphatase enzymes to its active moiety, ceftaroline. Its pharmacokinetic profile is summarized in **Table 2**.[16,17] Its volume of distribution is similar to that of the fourth-generation cephalosporin cefepime.

Ceftaroline is then hydrolyzed into its inactive metabolite, ceftaroline M-1. It undergoes little hepatic metabolism and lacks properties to make it a substrate, inhibitor, or inducer of the CYP450 enzyme system and therefore is not likely to cause notable CYP450-related drug-drug interactions.

Like most other beta-lactams, ceftaroline is primarily excreted by the kidneys. Furthermore, an estimated 21% of a dose is eliminated with each intermittent hemodialysis session. Therefore, renal and intermittent hemodialysis dose adjustments are necessary. The estimated elimination half-life is 2.6 hours, necessitating dosing two to three times daily, depending on the indication and infectious inoculum.

Ceftaroline dosing

Ceftaroline is available only in a parenteral preparation and is typically given at a dose of 600 mg every 12 hours.[10] The intravenous infusion is given over 1 hour.

The current stability data require reconstituted ceftaroline to be used within 6 hours at room temperature and within 24 hours if refrigerated.[10]

Ceftaroline requires dosing adjustments for patients with renal insufficiency. Per the manufacturer, renal dosing adjustments are based on the creatinine clearance rate, as estimated by the Cockroft-Gault formula:

- Creatinine clearance > 50 mL/min: no dosage adjustment necessary
- Creatinine clearance > 30 to ≤ 50 mL/min: give 400 mg every 12 hours
- Creatinine clearance ≥ 15 to ≤ 30 mL/min: give 300 mg every 12 hours
- Creatinine clearance < 15 mL/min or on intermittent dialysis: give 200 mg every 12 hours.

Ongoing clinical trials are investigating a higher-dosing strategy of 600 mg every 8 hours for patients with community-acquired bacterial pneumonia at risk of MRSA bacteremia.[18]

CLINICAL TRIALS LEADING TO CEFTAROLINE'S APPROVAL

Ceftaroline was approved for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin-structure infections due to susceptible pathogens on the basis of phase 3 comparator trials.

Community-acquired bacterial pneumonia: The FOCUS 1 and 2 trials

The efficacy and safety of ceftaroline in the treatment of community-acquired bacterial pneumonia was studied in two randomized, double-blind, noninferiority trials, known as Ceftaroline Community-acquired Pneumonia vs Ceftriaxone (FOCUS) 1 and FOCUS 2.[19,20]

Patients were adults and not critically ill, as was reflected by their being in Pneumonia Outcomes Research Team (PORT) risk class III or IV (with class V indicating the highest risk of death). Therefore, the results may not be completely applicable to critically ill patients or those not admitted to the hospital. Of note, patients were excluded from the trials if they had infections known or thought to be due to MRSA or to atypical organisms.[21] Baseline characteristics and patient demographics were similar between study groups in both trials.

A bacterial pathogen was identified in 26.1% of the patients included in the modified intent-to-treat analysis of the pooled data of the trials; the most common pathogens were *S pneumoniae*, methicillin-sensitive *S aureus*, *Haemophilus influenzae*, *K pneumoniae*, and *E coli*.[21]

Treatment. Patients received either ceftaroline 600 mg every 12 hours (or a lower dose based on renal function) or ceftriaxone 1 g every 24 hours. In addition, in the FOCUS 1 trial, patients in both treatment groups received clarithromycin 500 mg every 12 hours for the first day.[19]

Results. In both trials and in the integrated analysis, ceftaroline was noninferior to ceftriaxone (**Table 3**).[22] In the integrated analysis of both trials, compared with the ceftriaxone group, the ceftaroline group had a higher clinical cure rate among patients classified as PORT risk class III (86.8% vs 79.2%, weighted treatment difference 12.6%, 95% confidence interval [CI] 1.3–13.8) and among patients who had not received prior antibiotic treatment (85.5% vs 74.9%, weighted treatment difference 11.2%, 95% CI 4.5–18.0).[21]

TABLE 3

Ceftaroline: Clinical cure rates in community-acquired pneumonia

Trial	Ceftaroline % [a]	Ceftriaxone % [a]
FOCUS 1[19]	83.8	77.7
FOCUS 2[20]	81.3	75.5
Integrated analysis[21]	82.6 [b]	76.6

[a] Modified intent-to-treat analysis, based on "test-of-cure" assessment conducted 8–15 days after last dose.
[b] Statistically significant difference compared with ceftriaxone.

FOCUS = Ceftaroline Community-acquired Pneumonia vs Ceftriaxone trial

Acute bacterial skin and skin-structure infections: The CANVAS 1 and 2 trials

The efficacy and safety of ceftaroline in the treatment of complicated acute bacterial skin and skin-structure infections was studied in two randomized, double-blind trials: Ceftaroline Versus Vancomycin in Skin and Skin Structure Infections (CANVAS) 1 and CANVAS 2.[23,24]

Patients. Adult patients with a diagnosis of community-acquired skin and skin-structure infections warranting at least 5 days of intravenous antimicrobial therapy were included in the trials. Important protocol exclusions were patients with diabetic foot ulcers, decubitus ulcers, burns, ulcers associated with peripheral vascular disease accompanied by osteomyelitis, and suspected *P aeruginosa* infections.[25] This limits the external validity of ceftaroline use in the aforementioned excluded patient populations.

Patients in each treatment group of the trials had similar demographic characteristics. The most common infections were cellulitis, major abscess requiring surgical intervention, wound infection, and infected ulcer. Bacteremia was present in 4.2% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin-aztreonam group. The most common pathogen was *S aureus*. Methicillin resistance was present in 40% of the ceftaroline group and 34% of the control group.

Treatment. Patients received either ceftaroline 600 mg every 12 hours or the combination of vancomycin 1 g plus aztreonam 1 g given 12 hours, for 5 to 14 days.

Results. As assessed at a "test-of-cure" visit 8 to 15 days after the last dose of study medi-

Adjust doses of ceftaroline lower in patients with renal insufficiency

TABLE 4

Ceftaroline: Clinical cure rates in acute bacterial skin and skin-structure infections

Study	Ceftaroline % [a]	Vancomycin plus aztreonam % [a]
CANVAS 1[23]	86.6	85.6
CANVAS 2[24]	85.1	85.5
Integrated analysis[25]	85.9	85.5

[a] Modified intent-to-treat analysis, based on "test-of-cure" assessment conducted 8–15 days after last dose.

CANVAS = Ceftaroline Versus Vancomycin in Skin and Skin Structure Infections trial

cation, the efficacy of ceftaroline was similar to that of vancomycin-aztreonam, meeting the set noninferiority goal (**Table 4**).[25] Moreover, if assessed on day 2 or 3 (a new end point recommended by the FDA), the rate of cessation of erythema spread and absence of fever was higher in the ceftaroline group than in the vancomycin-aztreonam group.[26] However, this end point was not in the original trial protocol.

Guidelines on community-acquired pneumonia are being updated

CEFTAROLINE FOR OTHER INDICATIONS

As noted, ceftaroline has been approved for treating community-acquired bacterial pneumonia and acute bacterial skin and skin-structure infections. In addition, it has been used in several studies in animals, and case reports of non-FDA approved indications including endocarditis and osteomyelitis have been published. Clinical trials are evaluating its use in pediatric patients, as well as for community-acquired bacterial pneumonia with risk for MRSA and for MRSA bacteremia.

Endocarditis

Animal studies have demonstrated ceftaroline to have bactericidal activity against MRSA and hVISA in endocarditis.[27]

A few case series have been published describing ceftaroline's use as salvage therapy for persistent MRSA bacteremia and endocarditis. For example, Ho et al[28] reported using it in three patients who had endocarditis as a source of their persistent bacteremia. All three patients had resolution of their MRSA bloodstream infection following ceftaroline therapy. The dosage was 600 mg every 8 hours, which is higher than in the manufacturer's prescribing information.

Lin et al[29] reported using ceftaroline in five patients with either possible or probable endocarditis. Three of the five patients had clinical cure as defined by resolution or improvement of all signs and symptoms of infection, and not requiring further antimicrobial therapy.[29]

More data from clinical trials would be beneficial in defining ceftaroline's role in treating endocarditis caused by susceptible microorganisms.

Osteomyelitis

In animal studies of osteomyelitis, ceftaroline exhibited activity against MRSA in infected bone and joint fluid. Compared with vancomycin and linezolid, ceftaroline was associated with more significant decreases in bacterial load in the infected joint fluid, bone marrow, and bone.[30]

Lin et al[29] gave ceftaroline to two patients with bone and joint infections, both of whom had received other therapies that had failed. The doses of ceftaroline were higher than those recommended in the prescribing information; clinical cure was noted in both cases following the switch.

These data come from case series, and more study of ceftaroline's role in the treatment of osteomyelitis infections is warranted.

Meningitis

The use of ceftaroline in meningitis has been studied in rabbits. While ceftaroline penetrated into the cerebrospinal fluid in only negligible amounts in healthy rabbits (3% penetration), its penetration improved to 15% in animals with inflamed meninges. Ceftaroline cerebrospinal fluid levels in inflamed meninges were sufficient to provide bactericidal activity against penicillin-sensitive and resistant *S pneumoniae* strains as well as *K pneumoniae* and *E coli* strains.[31,32]

REPORTED ADVERSE EFFECTS OF CEFTAROLINE

Overall, ceftaroline was well tolerated in clinical trials, and its safety profile was similar to those of the comparator agents (ceftriaxone

and vancomycin-aztreonam).

As with the other cephalosporins, hypersensitivity reactions have been reported with ceftaroline. In the clinical trials, 3% of patients developed a rash with ceftaroline.[33,34] Patients with a history of beta-lactam allergy were excluded from the trials, so the rate of cross-reactivity with penicillins and with other cephalosporins is unknown.

In the phase 3 clinical trials, gastrointestinal side effects including diarrhea (5%), nausea (4%), and vomiting (2%) were reported with ceftaroline. *C difficile*-associated diarrhea has also been reported.[33]

As with other cephalosporins, ceftaroline can cause a false-positive result on the Coombs test. Approximately 11% of ceftaroline-treated patients in phase 3 clinical trials had a positive Coombs test, but hemolytic anemia did not occur in any patients.[33,34]

Discontinuation of ceftaroline due to an adverse reaction was reported in 2.7% of patients receiving the drug during phase 3 trials, compared with 3.7% with comparator agents.

WHEN SHOULD CEFTAROLINE BE USED IN DAILY PRACTICE?

Ceftaroline has been shown to be at least as effective as ceftriaxone in treating community-acquired bacterial pneumonia, and at least as effective as vancomycin-aztreonam in treating acute bacterial skin and skin-structure infections. The 2014 Infectious Diseases Society of America's guidelines for the diagnosis and management of skin and soft-tissue infections recommend ceftaroline as an option for empiric therapy for purulent skin and soft-tissue infections.[35]

The guidelines on community-acquired pneumonia have not been updated since 2007, which was before ceftaroline was approved. However, these guidelines are currently undergoing revision and may provide insight on ceftaroline's place in the treatment of community-acquired bacterial pneumonia.[36]

Currently, ceftaroline's routine use for these indications should be balanced by its higher cost ($150 for a 600-mg dose) compared with ceftriaxone ($5 for a 1-g dose) or vancomycin ($25 for a 1-g dose). The drug's in vitro activity against drug-resistant pneumococci and *S aureus*, including MRSA, hVISA, and VISA may help fill an unmet need or provide a safer and more tolerable alternative to currently available therapies.

However, ceftaroline's lack of activity against *P aeruginosa* and carbapenem-resistant Enterobacteriaceae does not meet the public health threat needs stemming from these multidrug-resistant microorganisms. Ongoing clinical trials in patients with more serious MRSA infections will provide important information about ceftaroline's role as an anti-MRSA agent.

While the discovery of antimicrobials has had one of the greatest impacts on medicine, continued antibiotic use is threatened by the emergence of drug-resistant pathogens. Therefore, it is as important as ever to be good stewards of our currently available antimicrobials. Developing usage and dosing criteria for antimicrobials based on available data and literature is a step forward in optimizing the use of antibiotics—a precious medical resource.

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