Therapeutics and Clinical Risk Management

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REVIEW

Critical appraisal of ceftaroline in the management of community-acquired bacterial pneumonia and skin infections

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
23 March 2012
Number of times this article has been viewed

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Abstract: Ceftaroline is a novel broad-spectrum cephalosporin β-lactam antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) as well as multidrug-resistant *Streptococcus pneumoniae* among other routine Gram positive and Gram negative organisms. It has been approved by the US Food and Drug Administration for treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSIs). Ceftaroline is approved for treatment of ABSSSI due to MRSA, however currently there are no data for pneumonia due to MRSA in humans. Herein we review the major clinical trials as well as ceftaroline microbiology, pharmacokinetics, and safety, followed by a look at further directions for investigation of this new agent.

Keywords: ceftaroline, pneumonia, skin infection

Introduction to clinical applications of ceftaroline

Ceftaroline fosamil (formerly T-91825) is the N-phosphorylated prodrug of ceftaroline (formerly PPI 0903M and TAK-499), a novel broad spectrum β-lactam antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) as well as *Streptococcus pneumoniae* with resistance to penicillin and other cephalosporins.[1–3] Based on two Phase III studies in community-acquired bacterial pneumonia (CABP)[4,5] and two Phase III studies in acute bacterial skin and skin structure infections (ABSSSIs),[6,7] ceftaroline received approval from the US Food and Drug Administration in 2010 for treatment of CAPB due to *S. pneumoniae* (including cases with concurrent bacteremia), methicillin-sensitive *S. aureus* (MSSA), *Haemophilus influenzae*, *H. parainfluenzae*, *Klebsiella pneumoniae*, and *Escherichia coli* as well as ABSSSI due to MSSA, MRSA, *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group, *Enterococcus faecalis* (ampicillin-susceptible isolates only), *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *Morganella morganii*. This article will discuss the trials resulting in this approval in further depth, as well as the mode of action, microbiology, pharmacokinetics, and safety and tolerability of ceftaroline, as well as advantages and disadvantages in comparison to alternate therapies.

Clinical issues in the management of CABP and ABSSSI

Community-acquired bacterial pneumonia

The FOCUS (ce**F**tar**O**line **C**ommunity-acquired pne**U**monia trial v**S** ceftriaxone in hospitalized patients) trials are two Phase III multicenter, randomized, double-blind

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trials comparing ceftaroline to ceftriaxone in CABP to demonstrate noninferiority.[4,5,8] Patients with CAPB with Pneumonia Outcomes Research Team (PORT) scores of III or IV were randomized to receive either ceftaroline 600 mg intravenously (IV) every 12 hours or ceftriaxone 1 g IV every 24 hours. Patients enrolled in either arm of FOCUS 1 also received two doses of clarithromycin 500 mg orally in the first 24 hours. Treatment was given for 5 to 7 days. Exclusion criteria included PORT class I, II, or V; intensive care unit admission at baseline; CABP suitable for outpatient therapy; confirmed or suspected health care-associated pneumonia pathogen; infection with a pathogen known to be resistant to study medication or high risk for such; high risk for MRSA or with Gram-positive cocci in clusters on sputum Gram stain; infection due to atypical pathogen (*Legionella*, *Mycoplasma*, *Chlamydophila* spp.); prior antimicrobial therapy within 96 hours; creatinine clearance ≤ 30 mL/min; elevated transaminases or bilirubin or other manifestation of end-stage liver disease; neutropenia or thrombocytopenia; empyema; and immunocompromise (chronic steroids, acquired immunodeficiency syndrome, etc). The primary outcome was to determine noninferiority in clinical cure rates at a test-of-cure visit 8–15 days post therapy in the clinically evaluable and modified intention-to-treat (MITT) groups. Secondary outcomes included cure in microbiologically evaluable (ME) and microbiological modified intention-to-treat (mMITT) groups (meaning at least one pathogen was isolated), cure at end of therapy, microbiological outcome at test-of-cure visit, overall success rate at test-of-cure visit, clinical and microbiological response by pathogen at test-of-cure visit, clinical relapse at a late follow-up visit (21–35 days after discontinuing study drug), microbiological reinfection/recurrence, and safety. A total of 1240 patients were randomized of whom 1228 received any drug. 614 each received ceftaroline and ceftriaxone. The two groups were similar in terms of baseline demographics, severity of pneumonia, comorbidities, and prior antibiotic use.

The clinical cure rate in the evaluable population was 84.3% in the ceftaroline group versus 77.7% in the ceftriaxone group (difference 6.7%, 95% confidence interval [CI]: 1.6%–11.8%). In the MITT group, cure rates were 82.6% and 76.6%, respectively (difference 6%, 95% CI: 1.4%–10.7%). For ME patients, cure rates were 85.1% versus 75.5% (difference 9.7, 95% CI: 0.7%–18.8%), and in the mMITT population, cure rates were 83.6% versus 75% (difference 8.7%, 95% CI: 0%–17.4%). All of these rates met noninferiority criteria, and all save the mMITT group reached numerical significance for the superiority of ceftaroline. For patients with *S. pneumoniae* infection, the cure rate for ceftaroline was 85.5% compared with 68.6% with ceftriaxone (difference 16.9%, no CI reported). For those with *S. aureus* infection including one patient with MRSA in the ceftriaxone arm, the cure rate was 72% versus 60% (difference 12%, no CI reported). In bacteremic patients, cure rates were 71.4% for ceftaroline compared with 58.8% for ceftriaxone (difference 12.6%, 95% CI: –17.6%–41.6%).

Acute bacterial skin and skin structure infections

In 2007, a Phase II randomized, observer-blinded trial of ceftaroline compared with vancomycin with or without aztreonam for ABSSSI was released.[9] The primary outcome of this study was clinical cure rate at a test-of-cure visit; a blinded investigator determined cure as resolution of signs and symptoms of ABSSSI or improvement such that no further therapy was needed. This trial included 100 patients, 67 in the ceftaroline arm and 33 in the comparator arm. Those on ceftaroline received 600 mg IV every 12 hours. Vancomycin was dosed at 1 g every 12 hours and aztreonam at 1 g every 8 hours. Patients were excluded if they had creatinine clearance ≤ 30 mL/min, >24 hours of antimicrobials in the preceding 96 hours, known vancomycin- or aztreonam-resistant pathogens including *Pseudomonas aeruginosa* or anaerobes, underlying osteomyelitis or septic arthritis, necrotizing fasciitis, human or animal bites, diabetic foot ulcers, gangrene, burns covering >5% of the body, mediastinitis, or required surgical intervention that could not be performed within 48 hours of initiating therapy. The two groups were similar in baseline demographics, types of infection, and microbes isolated. Cure rates in evaluable patients in both arms were comparable.

This study was followed by the two CANVAS (**C**eft**A**roli**N**e **V**ersus V**A**ncomycin in **S**kin and Skin Structure Infections) trials, Phase III multicenter, randomized, double blind studies again comparing ceftaroline to vancomycin with aztreonam for ABSSSI to demonstrate noninferiority.[6,7,10] In these identical trials patients with ABSSSI were randomized to receive ceftaroline 600 mg IV every 12 hours plus normal saline placebo or vancomycin 1 g every 12 hours with 1 g of aztreonam every 8 hours. Treatment was given for an average of 8 days. The primary outcome of these studies was clinical cure rate at test-of-cure visit in clinically evaluable and MITT populations. Secondary outcomes were microbiological response and clinical response at a test-of-cure visit at 8–15 days after the last dose of study drug and relapse/reinfection at a late follow up visit at 21–35 days after the last dose. Of 1396 randomized patients, 1378 received at least one dose of study drug; 1202 were clinically evaluable, and 914 were ME. The two groups were similar in demographic and infection data including sites of infection and area of involvement. In ME patients, *S. aureus* (MRSA and MSSA) was the most common pathogen.

The clinical cure rates in the evaluable groups were 91.6% for ceftaroline and 92.7% for vancomycin plus aztreonam (difference −1.1%, 95% CI: −4.2%–2%); in the MITT group the cure rates were 85.9% and 85.5%, respectively (difference 0.3%, 95% CI: −3.4%–4%). Cure rates were also comparable in ME patients, 92.7% versus 94.4% (difference −1.7%, 95% CI: −4.9%–1.6%). In bacteremic patients, cure rates were 84.6% in the ceftaroline group versus 100% in the vancomycin plus aztreonam group (difference −15.4%, 95% CI: −33.8%–1.5%). This difference was not statistically significant. Of note there was a higher rate of *S. aureus* bacteremia (both MRSA and MSSA) in the ceftaroline group (18 vs 9).

Ceftaroline: mode of action, microbiology, pharmacokinetics, safety, and tolerability

Mode of action

As with other β-lactam antibiotics, ceftaroline acts by binding penicillin-binding proteins (PBP) on the bacterial cell wall leading to perturbations in new wall formation as well as cell lysis.[1] These PBPs have a variety of structures and functions and different bacteria have different PBPs.[11] Ceftaroline was demonstrated after initial synthesis to have strong affinity for PBP 2a, a genetically altered PBP in MRSA.[1] Further in vitro research has again demonstrated strong affinity for PBP 2a-conferring activity against MRSA, as well as a high affinity for PBPs 1a, 2b, 2x, and 3, which are important PBPs in MSSA and *S. pneumoniae*.[12,13] These binding affinities were notably higher than those for oxacillin and ceftriaxone, standard antimicrobials for treatment of MSSA and *S. pneumoniae*, respectively.

Microbiology

Ceftaroline has a broad spectrum of activity which is represented in Table 1. Early in vitro testing demonstrated favorable minimum inhibitory concentration (MIC) against *S. aureus*, both MRSA and MSSA; *S. epidermidis* (methicillin-sensitive and -resistant strains); *S. pneumoniae,* including penicillin-resistant strains; and other streptococci.

Table 1 MIC ranges and MIC50–90 against selected pathogens.[2,3,16–18,20–29,33,34]

Organism	MIC Range	MIC50	MIC90
MSSA	≤0.008–1	0.12–0.25	0.25–0.5
MRSA	0.12–4	0.5–1	0.5–2
CONS	≤0.008–4	0.06–1	0.12–2
PSSP	≤0.008–0.25	≤0.008–0.015	≤0.016–0.06
PISP	≤0.008–0.5	0.015–0.13	0.006–0.13
PRSP	≤0.008–0.5	≤0.015–0.13	0.12–0.5
β-hemolytic streptococci	≤0.008–0.12	≤0.008–0.015	≤0.015–0.03
Viridans group streptococci	≤0.008–16	≤0.008–0.25	0.03–1
Enterococcus faecalis[a]	0.03–>32	1–4	4–16
Enterococcus faecium[a]	0.06–>128	1–>64	16–>128
Acinetobacter spp	≤0.003–>64	2–>64	8–>64
Citrobacter freundii	0.06–128	0.12–>16	2–64
Enterobacter spp[b]	≤0.008–>128	≤0.12–>32	0.5–>32
Escherichia coli[b]	≤0.008–>64	0.06–>32	0.12–>32
Klebsiella spp[b]	≤0.008–>32	0.06–>32	0.25–>32
Proteus spp	≤0.03–>32	0.06–>32	0.12–64
Salmonella spp	0.06–>32	0.12–0.13	0.25–>32
Haemophilus influenzae[c]	≤0.008–0.25	≤0.008–0.12	≤0.008–0.25
Moraxella catarrhalis	≤0.008–1	0.03–0.25	0.12–0.5
Pseudomonas aeruginosa	0.25–>128	16	>32
Serratia marcescens	0.015–>128	0.5–1	2–32
Bacteroides spp	0.03–>64	8–64	16–>64
Clostridium spp	≤0.008–64	0.06–2	0.25–16
Fusobacterium spp[d]	≤0.008–64	≤0.008–8	0.06–32
Propionibacterium acnes	≤0.008–0.125	≤0.008–0.03	0.06

Notes: [a]Includes vancomycin-susceptible and -resistant strains; [b]includes cephalosporin-sensitive and -resistant strains, as well as extended-spectrum β-lactamase-producing strains; [c]includes β-lactamase positive and negative strains; [d]all isolates with MIC > 0.5 are *F. mortiferum*.

Abbreviations: MIC, minimum inhibitory concentration; MIC50, MIC for 50% of isolates; MIC90, MIC for 90% of isolates; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; CONS, coagulase-negative *Staphylococcus*; PSSP, penicillin-sensitive *Streptococcus pneumoniae*; PISP, penicillin-intermediate *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*; spp, species.

Gram-negative pathogens with favorable MICs include *E. coli, Salmonella* spp., *K. oxytoca, K. pneumoniae, H. influenzae,* and *Moraxella catarrhalis*.[2] This spectrum has been confirmed against numerous pooled isolates in further in vitro testing.[3,14–21] Of note there is no activity against *P. aeruginosa* or extended spectrum β-lactamase (ESBL) producing Gram-negative organisms.[3] Ceftaroline has also demonstrated in vitro efficacy against a number of anaerobic bacteria, largely Gram-positive and β-lactamase-negative Gram-negative organisms.[22,23] It has been tested in several large samplings of pathogens causing CABP and ABSSSI with overall favorable results.[24–28]

One of the potential advantages of ceftaroline over other β-lactams is its activity against *S. aureus* isolates, including drug-resistant strains. In vitro testing against 152 strains of community-acquired MRSA from United States centers revealed the minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC90) of ceftaroline to be 0.5 μg/mL, a 64-fold increase in potency over ceftriaxone. These strains all had Panton–Valentine leukocidin genes and 67.8% were USA300 strains.[17] Activity of ceftaroline against MRSA and vancomycin-intermediate *S. aureus* has been confirmed in a hollow fiber model with ceftaroline demonstrating rapid bactericidal activity against these organisms.[19] Further in vitro and in vivo testing has demonstrated activity against a broad range of *S. aureus* isolates including vancomycin-intermediate, vancomycin-resistant, and daptomycin-nonsusceptible strains.[29–32]

Another therapeutic advantage of ceftaroline is its activity against a broad range of *S. pneumoniae* isolates, including penicillin-intermediate and -resistant strains. Initial in vitro testing demonstrated favorable MIC90 against penicillin-sensitive, -intermediate, and -resistant strains with ceftaroline MICs of 0.06 μg/mL, 0.13 μg/mL, and 0.25 μg/mL, respectively. These MICs are all favorable compared to ceftriaxone.[2] Ceftaroline has demonstrated in vitro efficacy against *S. pneumoniae* strains resistant to penicillin, amoxicillin, erythromycin, and cefotaxime,[15,33] showing superior in vitro activity to other β-lactams for cefotaxime-resistant strains.[34] This superiority to ceftriaxone in resistant isolates has been demonstrated in vivo as well.[35]

Pharmacokinetics

Ceftaroline fosamil undergoes rapid dephosphorylation to the active drug after infusion. In a Phase I study of a single IV dose of ceftaroline to healthy subjects, a dose-proportional concentration was attained.[36] In a 14 day IV dosing trial, the serum half-life of ceftaroline with 600 mg every 12-hour dosing was 2.6 hours with a maximal concentration of 21 μg/mL.[37] Dosing in patients with decreased renal function has demonstrated an increase in half-life (up to 4.6 hours in those with creatinine clearance averaging 38 mL/min), similar maximal concentration (31 μg/mL), but greatly increased area under the curve (120 hours*μg/mL versus 68 hours*μg/mL in those with normal renal function).[38] Therefore a dose reduction to 400 mg every 12 hours is recommended for those with creatinine clearance between 30–50 mL/min.[39] There are no data for those with creatinine clearance less than 30 mL/min or those on hemodialysis. These pharmacokinetics have been confirmed with population data from the ABSSSI and CABP studies.[40,41] In a post-hoc analysis of drug–drug interactions, ceftaroline levels were found to be modestly elevated in patients receiving CYP1A2 inhibitors, CYP3A4/5/7 inhibitors, and anionic drugs undergoing active renal secretion, but the effects of these increased levels are unclear.[42]

Safety and tolerability

Integrated safety data from the two FOCUS and two CANVAS trials show comparable adverse event (AE) rates to the control groups.[43,44] In the FOCUS studies, 47% of patients treated with ceftaroline had treatment-emergent AEs compared with 45.7% in the ceftriaxone group. Serious AEs were 11.3% versus 11.7%, discontinuations 4.4% versus 4.1%, and deaths 2.4% versus 2%. Only one death in each treatment group was felt by investigators to be related to study drug. In the ceftaroline group the most common AEs were diarrhea (4.2%), headache (3.4%), and insomnia (3.1%). There were more positive direct Coombs' tests in the ceftaroline group (9.8% versus 4.5%), but no difference in rate of anemia (0.8% versus 0.4%). Results were similar in the CANVAS trials with treatment-emergent AEs occurring in 44.7% of the ceftaroline group versus 47.5% of the vancomycin plus aztreonam group. Serious AEs were 4.3% versus 4.1%. The most common AEs in those receiving ceftaroline were nausea (5.9%), headache (5.2%), diarrhea (4.9%), and pruritis (3.5%). Similar to FOCUS data, in the CANVAS groups 11.5% of ceftaroline had positive direct Coombs' tests complared with 4.3% in the comparator arm, but there was no hemolytic anemia in either group. Among all four studies there were only three cases of *Clostridium difficile*-associated diarrhea, all in CANVAS patients; two were in the ceftaroline group and one in the vancomycin plus aztreonam group.

The advantages and disadvantages of ceftaroline in line with current therapy strategies

The largest of ceftaroline's potential advantages over other agents, particularly other β-lactams, is its activity against MRSA, a pathogen that has had a recent steady increase in incidence[45] as well as in antimicrobial resistance.[46] Overall cases of MRSA infection doubled from 1999–2005 from 127,036 hospital admissions in 1999 to 278,203 in 2005. MRSA has increased from 43% of *S. aureus* infection to 58% over this time period.[47] Based on active surveillance at several sites, in 2005 there were an estimated 94,360 cases of invasive MRSA infection in the United States with 18,650 deaths.[48] A majority (58.4%) of cases were community-onset in nature.

In the FOCUS studies, ceftaroline was compared head-to-head with ceftriaxone, which is a preferred agent in the Infectious Diseases Society of America (IDSA)/American Thoracic Society guidelines for treatment of CABP (along with a macrolide for coverage of atypical organisms).[49] In these noninferiority trials, ceftaroline was shown to be within the defined −10% performance range of ceftriaxone overall, and therefore noninferior. While ceftaroline did have numeric superiority in several populations including those in most of the defined study groups and subgroups,[8] given the design of these trials to test noninferiority and not superiority, ceftaroline cannot be called superior without further trials.

While not a traditional pathogen in CABP, MRSA is being recognized more and more frequently as a cause of severe pneumonia in otherwise healthy patients, as well as following influenza infection.[50–53] Ceftaroline has a demonstrated bactericidal effect in MRSA pneumonia in animal studies. Early models demonstrated a colony count decrease of more than 99.9% in neutropenic mice with MRSA pneumonia when treatment with ceftaroline was started one day after infection compared with no significant change in colony counts with similar timing of linezolid or vancomycin.[2] Of note, all three agents were equally effective when started only 2 hours after infection, but as MRSA is not a commonly thought of pathogen in CABP, directed anti-MRSA therapy is usually not initiated until following recovery of the organism. Further studies of ceftaroline for MRSA pneumonia are needed.

For ABSSSI, the current IDSA guidelines focus on Gram-positive coverage for cellulitis but specifically mention the growing problem of resistant *S. aureus* and *S. pyogenes* isolates in the selection of empiric therapy.[54] Indeed, in studies of microbiology of ABSSSI, MRSA is a predominant isolate. A prospective evaluation of patients with ABSSSI in an emergency department in northern California in 2003–2004 revealed over half to be infected with *S. aureus*; 75% of their staphylococcal isolates were MRSA.[55] In Atlanta in 2003, 72% of *S. aureus* isolates were MRSA; a majority of these were USA300 strains.[56] A 2008 prospective multicenter evaluation of purulent ABSSSI revealed 75% of these infections to be due to *S. aureus,* of which 79% were MRSA. 96% of these isolates were USA300.[57] As in the FOCUS trials, the CANVAS trials were designed to demonstrate noninferiority, an aim at which they were successful.[6,7,10] There is statistically significant improved outcome for ceftaroline over vancomycin plus aztreonam for ABSSSI in the United States study sites in the CANVAS 1 trial, but the trial had a small number of patients and the study was not designed for this particular outcome. Further testing particularly with USA300 infection is necessary. With Gram-negative-only infections, ceftaroline was statistically inferior with a cure rate of 85.3% versus 100%, but again the study had small numbers and this outcome was outside the study design.

Ceftaroline has had limited clinical use to demonstrate development of antimicrobial resistance, but in vitro serial passage studies have shown limited resistance induced in multiple Gram-positive and Gram-negative pathogens.[58] In this study no strains of *S. pneumoniae* or *S. aureus* demonstrated increased ceftaroline MIC after 50 daily serial passages. There was rare inducible resistance in *H. influenzae* and *E. faecalis*. There are no reports on development of resistance in the FOCUS and CANVAS trials.

Ceftaroline may eventually have a role in infections other than CABP and ABSSSI as well. Jacqueline et al initially demonstrated rapid bactericidal activity in vivo in a rabbit endocarditis model of infection due to MRSA and vancomycin-intermediate *S. aureus* (VISA), with comparable activity to vancomycin in MRSA infection and improved vegetation sterilization relative to vancomycin in VISA as well as favorable performance compared to linezolid in both strains.[59] More recently ceftaroline was compared with daptomycin and tigecycline in MSSA, MRSA, and glycopeptide-intermediate *S. aureus* (GISA). Ceftaroline was superior to tigecycline and equivalent to daptomycin in vegetation sterilization for all isolates.[30] Another animal study with ampicillin-sensitive *E. faecalis* endocarditis demonstrated improved bacterial killing and vegetation sterilization over vancomycin and linezolid in vancomycin-susceptible and vancomycin-resistant strains.[60] Current guidelines recommend ampicillin or penicillin plus gentamicin for these infections.[61] These animal endocarditis studies may provide the basis for further clinical evaluation, though so far, data in humans are lacking.

Ceftaroline has also demonstrated superiority to vancomycin and comparableness to linezolid in treatment of rabbit osteomyelitis due to MRSA and GISA.[62] Finally, ceftaroline has been shown to be superior to ceftriaxone in meningitis in rabbits due to penicillin-sensitive *S. pneumoniae* and a combination of ceftriaxone and vancomycin in penicillin-resistant *S. pneumoniae*.[63] Current guidelines recommend the combination of vancomycin and a third-generation cephalosporin for initial therapy of bacterial meningitis due to *S. pneumoniae*[64] Ceftaroline monotherapy may be further investigated for this application as well, though again, human data remain lacking to date.

One potential disadvantage of ceftaroline compared with other broad spectrum antibacterial agents is its lack of coverage of Gram-negative organisms, particularly those producing β-lactamases including AmpC, extended-spectrum β-lactamase (ESBL), and *K. pneumoniae* carbapenemase (KPC).[19] Ceftaroline has been combined with a novel β-lactamase inhibitor, NXL104, with excellent in vitro susceptibility data for bacteria with these β-lactamases. This combination when tested in vivo demonstrated bactericidal activity in a mouse thigh infection model.[65] Further pharmacodynamic modeling is being undertaken for the optimal dosing combination of these two agents.[66] This promising combination also bears further investigation for treatment of these very challenging infections.

Conclusion and place in therapy

Ceftaroline has a promising role in the future of infectious diseases. It has been labeled the first new drug in the IDSA's "10 × '20" initiative to have ten new antibiotics released by the year 2020.[67] However, it has several obstacles to overcome prior to routine use over current guideline recommendations. At present it is approved only for CABP and ABSSSI and has demonstrated only noninferiority as opposed to superiority to its comparators. The lack of clinical trial data in patients with MRSA pneumonia and bacteremia separate from ABSSSI and CABP in particular make it difficult to recommend ceftaroline over alternative therapies. Until there is more significant clinical experience, it can at least be counted among the dwindling array of options clinicians have to fight these increasingly resistant routine infections. Ceftaroline's potential for treatment of invasive infections due to MRSA and other resistant organisms is tantalizing and bears more investigation. It is hoped further clinical studies will illuminate the question mark looming over this otherwise promising new drug.

Disclosure

The authors report no conflicts of interest in this work.

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