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Ceftaroline Activity Tested against Bacterial Pathogens Frequently Isolated in United States (USA) Medical Centers: Results from 5 Years of AWARE Surveillance Program

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Abstract

Background: Ceftaroline (CPT) is a broad-spectrum cephalosporin with activity against *S. aureus* (SA), including MRSA, multidrug-resistant *S. pneumoniae* (SPN) and wildtype Enterobacteriaceae (ENT). The AWARE Program monitors the in vitro activity of CPT against clinical bacteria from various infection types. We evaluated the activity of CPT against prevalent Gram-positive and -negative species isolated in USA hospitals.

Methods: A total of 84,704 isolates were consecutively collected (one per patient) from 191 medical centers in 2009-2013 and tested for susceptibility (S) to CPT and comparator agents using CLSI broth microdilution methods.

Results: Isolates were mainly from skin and soft tissue (27,395; 32.3%), respiratory tract (23,931; 28.3%) and bloodstream (17,685; 20.9%) infections. CPT inhibited all SA strains (49.7% MRSA) at ≤2 µg/mL and was very active against MRSA (MIC_{90}, 1 µg/mL; 97.6% S; Table). CPT was 16- and >32-fold more active than ceftriaxone (CRO) against methicillin-S SA and MRSA, respectively. CPT inhibited all SPN at ≤0.5 µg/mL (100.0% S) and remained active against MDR SPN, including CRO-non-S (9.4% at ≥2 µg/mL) strains. CPT activity against the most common ENT (MIC_{50}, 0.12 µg/mL; 78.9% S) was similar to CRO (MIC_{50}, ≤0.25 µg/mL; 86.8% S) and ceftazidime (MIC_{50}, 0.12 µg/mL; 89.7% S). ESBL phenotypes were observed in 11.8% of *E. coli* and 14.7% of *Klebsiella* spp., and all cephalosporins showed limited activity against ESBL-phenotype strains. *H. influenzae* (MIC_{90}, 0.03 µg/mL; 100.0% S), *H. parainfluenzae* (MIC_{90}, 0.03 µg/mL) and *M. catarrhalis* (MIC_{90}, 0.12 µg/mL) strains were highly CPT-S, independent of β-lactamase production.

Conclusions: CPT demonstrated enhanced and consistent (2008-2013) activity against staphylococci, including MRSA, different streptococcal groups, and *Haemophilus* spp. CPT also had an activity against ENT most similar to that of currently available broad-spectrum cephalosporins.

Introduction

Ceftaroline fosamil (Teflaro®), prodrug of ceftaroline, was approved in 2010 by the United States (USA) Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infection (ABSSSI) due to susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and -resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *K. oxytoca*. Ceftaroline fosamil was also approved for community-acquired bacterial pneumonia (CABP) due to *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *S. aureus* (MSSA only), *Haemophilus influenzae, K. pneumoniae, K. oxytoca,* and *E. coli.*

An antimicrobial resistance surveillance program, known as the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, was designed to monitor the activity of ceftaroline and comparator agents. This program provides contemporary and longitudinal information on the activity of this newly released agent against relevant pathogens. We report the in vitro activity of ceftaroline against bacterial organisms isolated in USA medical centers during a 5-year period (2009-2013) as part of the USA AWARE Program.

Methods

Organisms collection: A total of 84,704 bacterial isolates were consecutively collected from clinical infections through the AWARE program in 2009-2013. One hundred eighty nine medical centers distributed across all nine USA Census Regions contributed clinical isolates. The isolates were from skin and skin structure infections (27,395; 32.3%), respiratory tract infections (23,931; 28.3%), bloodstream infections (17,685; 20.9%), urinary tract infections (7,814; 9.2%), intra-abdominal infections (1,521; 1.8%) and other sites (6,358; 7.5%). Isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, Iowa, USA) for reference susceptibility testing. Only one strain per patient infection episode was included in the surveillance.

Susceptibility testing: Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012) and CLSI interpretations were based on M100-S24 and M45-A2 breakpoints. Streptococcal isolates were tested in Mueller-Hinton broth supplemented with 2.5-5% lysed horse blood, and *Haemophilis* spp. isolates were tested in Haemophilus Test Media, whereas all other organisms were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control strains assured proper test conditions.

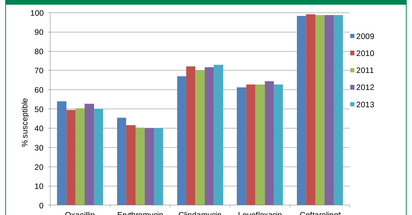
Results

- MRSA overall rate was 49.7%, varying from a low of 46.0% in 2009 to a high of 50.5% in 2010, with no trend toward increase or decrease during the study period (Figure 1).
- *S. aureus* (MIC_{90}, 1 µg/mL), including MRSA (MIC_{90}, 1 µg/mL), and coagulase-negative staphylococci (MIC_{90}, 0.5 µg/mL) were particularly susceptible to ceftaroline (Tables 1 and 2).
- Ceftaroline inhibited 98.8% of *S. aureus* strains at the susceptible breakpoint of ≤1 µg/mL (Tables 1 and 2). Susceptibility rates to levofloxacin and clindamycin were 60.2 and 71.1%, respectively, according to CLSI breakpoints. Daptomycin, linezolid, tigecycline, and vancomycin showed >99.9% susceptibility (data not shown).
- Overall, 97.6% of MRSA (12,514 strains tested) were susceptible to ceftaroline ($MIC_{50/90}$, 0.5/1 µg/mL; highest MIC, 2 µg/mL; Table 1). When tested against MSSA, ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/mL; Table 1) was 16-fold more potent than ceftriaxone (MIC_{50} and MIC_{90}, 4 µg/mL; data not shown).
- Ceftaroline ($MIC_{50/90}$, ≤0.015/0.12 µg/mL) inhibited all (100.0%) 10,096 *S. pneumoniae* strains at the MIC of ≤0.5 µg/mL, which is the susceptible breakpoint established the CLSI and USA-FDA (Table 2), and showed potent activity against ceftriaxone-non-susceptible strains (n=952; MIC_{50} and MIC_{90}, 0.25 µg/mL; Table 1 and Figures 2 and 3). Susceptibility to ceftriaxone ($MIC_{50/90}$, ≤0.25/1 µg/mL; Figure 3) and amoxicillin/clavulanate ($MIC_{50/90}$, ≤1/8 µg/mL) were 90.6 and 84.9%, respectively (data not shown).
- Ceftaroline was very potent against β-hemolytic streptococci (MIC_{50} and MIC_{90}, ≤0.015 µg/mL; highest MIC, 0.12 µg/mL; 100.0% susceptible; Tables 1 and 2) and viridans group streptococci ($MIC_{50/90}$, 0.03/0.06 µg/mL; Table 1).
- Ceftaroline activity against Enterobacteriaceae strains ($MIC_{50/90}$, 0.12/>32 µg/mL; 78.9% susceptible; Tables 1 and 2) was similar to that of ceftriaxone ($MIC_{50/90}$, ≤0.25/8 µg/mL; 86.8% susceptible) and ceftazidime ($MIC_{50/90}$, 0.12/8 µg/mL; 89.7% susceptible; data not shown). Non-ESBL phenotype strains were generally susceptible to ceftaroline, whereas ESBL-producing strains had elevated ceftaroline MIC values (Table 1).
- ESBL phenotypes were observed in 11.8% of *E. coli* and 14.7% of *Klebsiella* spp., and all cephalosporins showed limited activity against ESBL-phenotype strains (data not shown).
- Ceftaroline inhibited all (100.0%) *H. influenzae* strains (3,906; 25.2% β-lactamase producers) at MIC of 0.5 µg/mL or less (Tables 1 and 2 and Figure 4). Ceftaroline was also active against *H. parainfluenzae* ($MIC_{50/90}$, ≤0.015/0.03 µg/mL) and *M. catarrhalis* ($MIC_{50/90}$, 0.06/0.12 µg/mL) strains, independent of β-lactamase production (Table 1).

Table 1. Summary of ceftaroline activity tested against 84,704 bacterial isolates from USA medical centers (2009-2013)

Organism	No. of Isolates	no. of isolates (cumulative %) inhibited at ceftaroline MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	MIC_{50}	MIC_{90}
Staphylococcus aureus	25192	4 (0.0)	9 (0.1)	64 (0.3)	1193 (5.0)	11035 (48.8)	6931 (76.4)	5656 (98.8)	300 (100.0)	--	--	--	--	0.5	1
MSSA	12678	4 (0.0)	9 (0.1)	64 (0.6)	1183 (9.9)	10832 (95.4)	583 (>99.9)	3 (100.0)	--	--	--	--	--	0.25	0.25
MRSA	12514	--	--	--	10 (0.1)	203 (1.7)	6348 (52.4)	5653 (97.6)	300 (100.0)	--	--	--	--	0.5	1
Coagulase-negative staphylococci	3379	32 (0.9)	90 (3.6)	683 (23.8)	513 (39.0)	1184 (74.0)	788 (97.4)	79 (99.7)	10 (100.0)	--	--	--	--	0.25	0.5
Staphylococcus epidermidis	1453	4 (0.3)	37 (2.8)	335 (25.9)	139 (35.4)	529 (71.9)	383 (98.2)	26 (100.0)	--	--	--	--	--	0.25	0.5
Staphylococcus haemolyticus	99	--	--	--	23 (23.2)	30 (53.5)	25 (78.8)	16 (94.9)	5 (100.0)	--	--	--	--	0.25	1
Staphylococcus hominis	167	--	2 (1.2)	9 (6.6)	58 (41.3)	40 (65.3)	52 (96.4)	6 (100.0)	--	--	--	--	--	0.25	0.5
Enterococcus faecalis	2315	--	--	--	3 (0.1)	12 (0.6)	49 (2.8)	582 (27.9)	1092 (75.1)	229 (85.0)	305 (98.1)	31 (99.5)	12 (100.0)	2	8
Streptococcus pneumoniae	10096	6186 (61.3)	902 (70.2)	916 (79.3)	1441 (93.6)	573 (99.2)	78 (100.0)	--	--	--	--	--	--	≤0.015	0.12
Penicillin-S (MIC, ≤2 µg/mL)	8937	6186 (69.2)	902 (79.3)	907 (89.5)	907 (99.6)	33 (>99.9)	2 (100.0)	--	--	--	--	--	--	≤0.015	0.12
Penicillin-I (MIC, 4 µg/mL)	1042	--	--	8 (0.8)	531 (51.7)	467 (96.5)	36 (100.0)	--	--	--	--	--	--	0.12	0.25
Penicillin-R (MIC, ≥8 µg/mL)	117	--	--	1 (0.9)	3 (3.4)	73 (65.8)	40 (100.0)	--	--	--	--	--	--	0.25	0.5
Ceftriaxone-non-S. (MIC, ≥2 µg/mL)	952	1 (0.1)	3 (0.4)	5 (0.8)	365 (39.3)	501 (91.9)	77 (100.0)	--	--	--	--	--	--	0.25	0.25
Viridans group streptococci	2332	1136 (48.7)	747 (80.7)	250 (91.5)	91 (95.4)	49 (97.5)	43 (99.3)	16 (100.0)	--	--	--	--	--	0.03	0.06
Streptococcus anginosus	371	142 (38.3)	209 (94.6)	19 (99.7)	0 (99.7)	1 (100.0)	--	--	--	--	--	--	--	0.03	0.03
β-haemolytic streptococci	5679	5162 (90.9)	497 (99.6)	19 (>99.9)	1 (100.0)	--	--	--	--	--	--	--	--	≤0.015	≤0.015
Streptococcus pyogenes	2166	2155 (99.5)	8 (99.9)	2 (100.0)	1 (100.0)	--	--	--	--	--	--	--	--	≤0.015	≤0.015
Streptococcus agalactiae	2873	2465 (85.8)	405 (99.9)	3 (100.0)	--	--	--	--	--	--	--	--	--	≤0.015	0.03
Enterobacteriaceae	25139	139 (0.6)	1251 (5.5)	6443 (31.2)	6578 (57.3)	3259 (70.3)	2161 (78.9)	1294 (84.0)	453 (85.8)	301 (87.0)	273 (88.1)	303 (89.3)	2684 (100.0)	0.12	>16
Escherichia coli	8287	76 (0.9)	744 (9.9)	2645 (41.8)	2164 (67.9)	902 (78.8)	480 (84.6)	223 (87.3)	86 (88.3)	55 (89.0)	60 (89.7)	58 (90.4)	794 (100.0)	0.12	16
Klebsiella spp.	7381	34 (0.5)	263 (4.0)	2198 (33.8)	2110 (62.4)	963 (75.4)	514 (82.4)	207 (85.2)	60 (86.0)	60 (86.8)	55 (87.6)	51 (88.3)	866 (100.0)	0.12	>16
Proteus mirabilis	1883	2 (0.1)	35 (2.0)	650 (36.5)	771 (77.4)	184 (87.2)	97 (92.4)	37 (94.3)	17 (95.2)	8 (95.6)	4 (95.9)	14 (96.6)	64 (100.0)	0.12	0.5
Enterobacter cloacae	2465	12 (0.5)	35 (1.9)	112 (6.5)	622 (31.7)	695 (59.9)	309 (72.4)	95 (76.3)	39 (77.8)	25 (78.9)	33 (80.2)	52 (82.3)	436 (100.0)	0.25	>16
Enterobacter aerogenes	894	3 (0.3)	21 (2.7)	309 (37.2)	268 (67.2)	58 (73.7)	32 (77.3)	17 (79.2)	11 (80.4)	11 (81.7)	9 (82.7)	22 (85.1)	133 (100.0)	0.12	>16
Morganella morganii	911	8 (0.9)	74 (9.0)	253 (36.8)	182 (56.8)	74 (64.9)	57 (71.1)	26 (74.0)	24 (76.6)	22 (79.0)	23 (81.6)	23 (84.1)	145 (100.0)	0.12	>16
Citrobacter koseri	514	3 (0.6)	7 (1.9)	156 (32.3)	251 (81.1)	31 (87.2)	41 (95.1)	13 (97.7)	2 (98.1)	2 (98.4)	1 (98.6)	1 (98.8)	6 (100.0)	0.12	0.5
Citrobacter freundii	574	--	1 (0.2)	11 (2.1)	146 (27.5)	211 (64.3)	61 (74.9)	9 (76.5)	4 (77.2)	5 (78.0)	6 (79.1)	18 (82.2)	102 (100.0)	0.25	>16
Serratia marcescens	1378	--	1 (0.1)	1 (0.1)	3 (0.4)	71 (5.5)	467 (39.4)	541 (78.7)	134 (88.4)	47 (91.8)	45 (95.1)	24 (96.8)	44 (100.0)	1	4
Proteus vulgaris	305	--	3 (1.0)	7 (3.3)	8 (5.9)	41 (19.3)	50 (35.7)	53 (53.1)	30 (63.0)	25 (71.1)	14 (75.7)	17 (81.3)	57 (100.0)	1	>16
Providencia spp.	547	1 (0.2)	67 (12.4)	101 (30.9)	53 (40.6)	29 (45.9)	53 (55.6)	73 (68.9)	46 (77.3)	41 (84.8)	23 (89.0)	23 (93.2)	37 (100.0)	0.5	16
Pseudomonas aeruginosa	4115	--	--	--	--	4 (0.1)	19 (0.6)	46 (1.7)	104 (4.2)	260 (10.5)	781 (29.5)	1150 (57.4)	1751 (100.0)	16	>16
Acinetobacter baumannii	632	--	--	--	--	--	3 (0.5)	19 (3.5)	72 (14.9)	86 (28.5)	63 (38.4)	17 (41.1)	372 (100.0)	>16	>16
Haemophilus influenzae	3906	3403 (87.1)	386 (97.0)	87 (99.2)	22 (99.8)	6 (99.9)	2 (100.0)	--	--	--	--	--	--	≤0.015	0.03
β-lactamase-negative	2921	2701 (92.5)	202 (99.4)	16 (99.9)	2 (100.0)	--	--	--	--	--	--	--	--	≤0.015	≤0.015
β-lactamase-positive	985	702 (71.3)	184 (89.9)	71 (97.2)	20 (99.2)	6 (99.8)	2 (100.0)	--	--	--	--	--	--	≤0.015	0.06
Haemophilus parainfluenzae	408	354 (86.8)	29 (93.9)	10 (96.3)	8 (98.3)	2 (98.8)	3 (99.5)	1 (99.8)	1 (100.0)	--	--	--	--	≤0.015	0.03
Moraxella catarrhalis	1511	185 (12.2)	379 (37.3)	481 (69.2)	354 (92.6)	100 (99.2)	10 (99.9)	2 (100.0)	--	--	--	--	--	0.06	0.12

Figure 1. Yearly susceptibility rates among *S. aureus* from the AWARE Program (n=25,192; 2009-2013)



* All non-susceptible isolates showed a ceftaroline MIC of 2 µg/mL (intermediate). Ceftaroline resistant (MIC, ≥4 µg/mL) isolates were not detected during study period.

Figure 2. Yearly susceptibility rates for *S. pneumoniae* (n=10,096; 2009-2013)

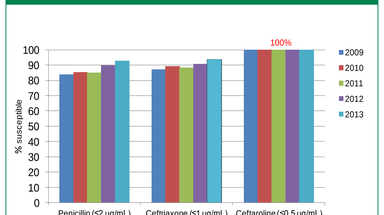
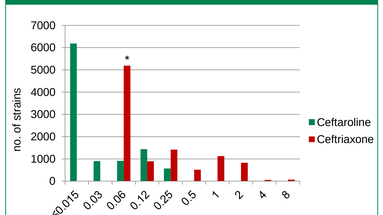


Figure 3. Ceftaroline and ceftriaxone activity tested against *S. pneumoniae* (n=10,096; 2009-2013)



* Indicates number of strains with ceftriaxone MIC of ≤0.06 µg/mL

Figure 4. Ceftaroline activity tested against *H. influenzae* (n=931; 2013)

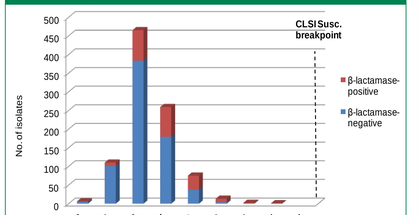


Table 2. Interpretive criteria for ceftaroline according to USA-FDA and CLSI breakpoint criteria (Teflaro Package Insert, 2012; CLSI, 2014)

Organism	Breakpoint (µg/mL) Susceptible	Resistant
S. aureus	≤1	≥4
S. pneumoniae	≤0.5	ND[a]
S. agalactiae	≤0.5	ND
S. pyogenes	≤0.5	ND
H. influenzae	≤0.5	ND
Enterobacteriaceae	≤0.5	≥2

a. ND = not defined

Conclusions

- Ceftaroline demonstrated enhanced and consistent (2009-2013) in vitro activity against staphylococci, including MRSA, different streptococcal groups, and *Haemophilus* spp.
- Ceftaroline also had an in vitro activity against Enterobacteriaceae most similar to that of currently available broad-spectrum cephalosporins.

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