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Evaluation of the *In Vitro* Activity of Ceftaroline Tested against Clinical Bacterial Isolates from USA Hospitals: Results from 5 Years of the AWARE Surveillance Program (2011-2015)

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Abstract

Background: Ceftaroline (CPT) is a broad-spectrum cephalosporin with activity against *S. aureus* (SA), including methicillin-resistant SA (MRSA), multidrug-resistant (MDR) *S. pneumoniae* (SPN) and wild-type Enterobacteriaceae (ENT). CPT fosamil was approved for clinical use in the USA in October 2010, and the AWARE Program monitors its *in vitro* activity 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 114,131 isolates were consecutively collected (one/patient) from 183 medical centers in 2011-2015 and tested for susceptibility (S) to CPT and comparator agents using CLSI broth microdilution methods.

Results: Isolates were mainly collected from skin/soft tissue (38,183; 33.5%), respiratory tract (33,553; 29.4%) and bloodstream (17,298; 15.2%) infections. MRSA rates varied from a high of 49.9% in 2013 to a low of 44.9% in 2015 (48.7% overall). CPT inhibited all SA strains at ≤2 µg/mL and was very active against MRSA ($MIC_{50/90}$, 0.5/1 µg/mL; 97.2% S; see Table 1). CPT was 16-fold more active than ceftriaxone (CRO) against methicillin-S SA (MSSA). CPT inhibited 99.99% of SPN at ≤0.5 µg/mL (only 1 non-S isolate of 11,696 had a CPT MIC of 1 µg/mL) and remained active against MDR SPN, including CRO-non-S (7.2% at ≥2 µg/mL) strains. SPN S rates to CRO (≤1 µg/mL) increased from 88.4% in 2011 to 98.1% in 2015. CPT activity against the most common ENT (MIC_{50}, 0.12 µg/mL; 78.8% S) was similar to CRO (MIC_{50}, ≤0.06 µg/mL; 85.8% S). The highest CPT MIC value among β-hemolytic streptococci was 0.06 µg/mL. ESBL phenotypes were observed in 13.4% of *E. coli* and 14.8% of *Klebsiella* spp., and all cephalosporins showed limited activity against ESBL-phenotype strains. *H. influenzae* (MIC_{90}, 0.03 µg/mL; >99.9% S), *H. parainfluenzae* (MIC_{90}, 0.03 µg/mL) and *M. catarrhalis* (MIC_{90}, 0.12 µg/mL) isolates were highly CPT-S, independent of β-lactamase production.

Conclusions: CPT demonstrated potent and consistent (2011-2015) 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 (US-FDA) for the treatment of adult with 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.* Approval for treating pediatric patients 2 months of age and older was granted in 2016. Furthermore, the clinical studies section of the ceftaroline fosamil label has been updated to include data from the Phase 3 ABSSSI studies for patients with baseline *S. aureus* bacteremia. Ceftaroline fosamil is 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 and 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 antimicrobial agent against relevant pathogens. We report the *in vitro* activity of ceftaroline against bacterial organisms isolated in USA medical centers since it was initially approved by the US-FDA (2011-2015).

Methods

Organism collection:
A total 114,131 isolates were consecutively collected (one per infection episode) from 183 medical centers from January 2011 to December 2015 as part of the AWARE Program. The isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, Iowa, USA) for reference susceptibility testing.

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-A10 (2015), and CLSI interpretations were based on M100-S26 breakpoints. Streptococcal isolates were tested in Mueller-Hinton broth supplemented with 2.5-5% lysed horse blood, and *Haemophilus* spp. isolates were tested in Haemophilus Test Media (HTM), whereas all other organisms were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains assured proper test conditions.

Results

- Isolates were collected from skin and skin structure infections (38,183; 33.5%), pneumonia in hospitalized patients (25,073; 22.0%), bloodstream infections (17,298; 15.2%), community-acquired respiratory tract infections (8,480; 7.4%), urinary tract infections (13,581; 11.9%), intra-abdominal infections (3,353; 2.9%) and other infection types (8,163; 7.2%).
- Ceftaroline inhibited all *S. aureus* isolates (n=33,181; $MIC_{50/90}$, 0.5/1 µg/mL; 98.6% susceptible) at ≤2 µg/mL and was very active against MRSA (n=16,157; $MIC_{50/90}$, 0.5/1 µg/mL; 97.2% susceptible; Table 1 and Figure 1).
- MRSA rates varied from a high of 49.9% in 2013 to a low of 44.9% in 2015 (48.7% overall; Figure 2).
- Ceftaroline ($MIC_{50/90}$, 0.25/0.25 µg/mL; Table 1) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 µg/mL; data not shown) against methicillin-susceptible *S. aureus* (MSSA; n=17,024).
- Ceftaroline inhibited 99.99% of *S. pneumoniae* at ≤0.5 µg/mL (only 1 non-susceptible isolate of 11,696 had a ceftaroline MIC of 1 µg/mL), and remained active against multidrug-resistant *S. pneumoniae*, including ceftriaxone-non-susceptible (n=836; $MIC_{50/90}$, 0.25/0.25 µg/mL; 99.9% susceptible) strains (Table 1 and Figure 3).
- When tested against penicillin-resistant (MIC, ≥8 µg/mL) strains (n=81), ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/mL; Table 1) was eight- to 16-fold more potent than ceftriaxone ($MIC_{50/90}$, 2/8 µg/mL; data not shown).
- *S. pneumoniae* susceptibility rates to ceftriaxone (≤1 µg/mL) increased from 88.4% in 2011 to 98.1% in 2015 (Figure 2).
- Ceftaroline activity against the most common Enterobacteriaceae ($MIC_{50/90}$, 0.12/32 µg/mL; 78.8% susceptible; Table 1) was similar to ceftriaxone ($MIC_{50/90}$, ≤0.06 µg/mL; 85.8% susceptible; data not shown).
- β-hemolytic streptococcal isolates (n=5,537) were highly susceptible to ceftaroline ($MIC_{50/90}$, ≤0.015/≤0.015 µg/mL). The highest ceftaroline MIC value was 0.03 µg/mL for *S. pyogenes* and 0.06 µg/mL for *S. agalactiae* and *S. dysgalactiae* (Table 1).
- ESBL phenotypes were observed in 13.4% of *E. coli* and 14.8% of *Klebsiella* spp. overall; Table 1). Among *E. coli*, the ESBL phenotype rate increased from 12.1% in 2011 to 15.1% in 2015, whereas among *K. pneumoniae*, ESBL phenotype rates remained more stable during the years of the study (Figure 2). All cephalosporins showed limited activity against ESBL-phenotype strains (data not shown).
- *H. influenzae* ($MIC_{90/90}$, ≤0.015/0.03 µg/mL; >99.9% susceptible), *H. parainfluenzae* ($MIC_{50/90}$, ≤0.015/0.03 µg/mL) and *M. catarrhalis* ($MIC_{50/90}$, 0.06/0.12 µg/mL) isolates were highly susceptible to ceftaroline, independent of β-lactamase production (Table 1).

Figure 1. Ceftaroline activity against *S. aureus* (n=33,181)

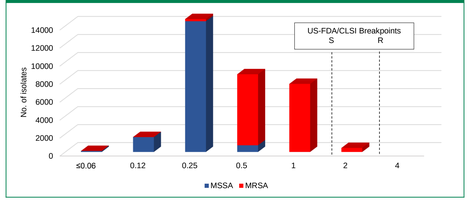


Table 1. Summary of ceftaroline activity tested against 114,131 bacterial isolates from US medical centers (2011-2015).

Organism/Organism Group (no. total)	Number of isolates (cumulative %) inhibited at ceftaroline MIC (µg/mL) of:													MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	(µg/mL)	
S. aureus (33,181)			112 (0.3)	1662 (5.3)	14758 (49.8)	8633 (75.8)	7568 (98.6)	448 (100.0)						0.5	1
MSSA (17,024)			111 (0.7)	1651 (10.4)	14519 (95.6)	742 (>99.9)	1 (100.0)							0.25	0.25
MRSA (16,157)			1 (<0.1)	11 (0.1)	239 (1.6)	7891 (50.4)	7567 (97.2)	448 (100.0)						0.5	1
CoNS (4,276)			1012 (23.7)	715 (40.4)	1486 (75.1)	923 (96.7)	113 (99.4)	25 (>99.9)	2 (100.0)					0.25	0.5
S. pneumoniae (11,696)	7274 (62.2)	1103 (71.6)	1159 (81.5)	1649 (95.6)	455 (99.5)	55 (>99.9)	1 (100.0)							≤0.015	0.12
PEN-S (≤2 µg/mL; 10,696)	7274 (68.0)	1103 (78.3)	1153 (89.1)	1123 (99.6)	40 (>99.9)	3 (100.0)								≤0.015	0.12
PEN-I (4 µg/mL; 919)			6 (0.7)	524 (57.7)	365 (97.4)	24 (100.0)								0.12	0.25
PEN-R (≥8 µg/mL; 81)				2 (2.5)	50 (64.2)	28 (98.8)	1 (100.0)							0.25	0.5
CRO-NS (≥2 µg/mL; 836)		3 (0.4)	8 (1.3)	356 (43.9)	414 (93.4)	54 (99.9)	1 100.0)							0.25	0.25
Viridans group streptococci (2,335)	1177 (50.4)	747 (82.4)	248 (93.0)	90 (96.9)	33 (98.3)	31(99.6)	9 (100.0)							≤0.015	0.06
β-haemolytic streptococci (5,537)	5266 (95.1)	269 (>99.9)	2(100.0)											≤0.015	≤0.015
S. pyogenes (2,304)	2292 (99.5)	12 (100.0)												≤0.015	≤0.015
S. agalactiae (2,814)	2558 (90.9)	255 (>99.9)	1(100.0)											≤0.015	≤0.015
S. dysgalactiae (419)	416 (99.3)	2 (99.8)	1(100.0)											≤0.015	≤0.015
Enterobacteriaceae (37,814)	303 (0.8)	2454 (7.3)	9523 (32.5)	9659 (58.1)	4790 (70.8)	3036 (78.8)	1781 (83.5)	676 (85.3)	443 (86.5)	433 (87.6)	500 (88.9)	493 (90.2)	3687 (100.0)	0.12	32
E. coli (12,682)	201 (1.6)	1500 (13.4)	3912 (44.3)	3148 (69.1)	1217 (78.7)	642 (83.7)	278 (85.9)	124 (86.9)	90 (87.6)	97 (88.4)	103 (89.2)	62 (89.7)	1308 (100.0)	0.12	>32
non-ESBL-phenotype (10,979)	201 (1.8)	1500 (15.5)	3909 (51.1)	3128 (79.6)	1179 (90.3)	617 (95.9)	266 (98.4)	106 (99.3)	40 (99.7)	21 (99.9)	8 (>99.9)	4 (100.0)		0.06	0.25
ESBL-phenotype (1,703)			3 (0.2)	20 (1.4)	38 (3.6)	25 (5.0)	12 (5.8)	18 (6.8)	50 (9.7)	76 (14.2)	95 (19.8)	58 (23.2)	1308 (100.0)	>32	>32
Klebsiella spp. (10,084)	48 (0.5)	458 (5.0)	2967 (34.4)	2894 (63.1)	1337 (76.4)	652 (82.9)	233 (85.2)	81 (86.0)	64 (86.6)	78 (87.4)	69 (88.1)	62 (88.7)	1141 (100.0)	0.12	>32
non-ESBL-phenotype (8,593)	48 (0.6)	458 (5.9)	2967 (40.4)	2894 (74.1)	1337 (89.7)	643 (97.1)	206 (99.5)	27 (99.8)	5 (99.9)	4 (>99.9)	2 (>99.9)	2 (100.0)		0.12	0.5
ESBL-phenotype (1,491)						9 (0.6)	27 (2.4)	54 (6.0)	59 (10.0)	74 (15.0)	67 (19.5)	60 (23.5)	1141 (100.0)	>32	>32
K. pneumoniae (7,972)	45 (0.6)	403 (5.6)	2666 (39.1)	2287 (67.7)	728 (76.9)	392 (81.8)	173 (84.0)	71 (84.9)	55 (85.5)	63 (86.3)	54 (87.0)	48 (87.6)	987 (100.0)	0.12	>32
K. oxytoca (2,108)	3 (0.1)	55(2.8)	301 (17.0)	607 (45.8)	606 (74.6)	260 (86.9)	60 (89.8)	10 (90.2)	9 (90.7)	15 (91.4)	15 (92.1)	14 (92.7)	153 (100.0)	0.25	2
P. mirabilis (2,907)	5 (0.2)	136 (4.9)	1061 (41.3)	1109 (79.5)	266 (88.6)	115 (92.6)	38 (93.9)	19 (94.6)	11 (94.9)	11 (95.3)	28 (96.3)	16 (96.8)	92 (100.0)	0.12	0.5
E. cloacae (4,053)	20 (0.5)	59 (1.9)	249 (8.1)	1074 (34.6)	1098 (61.7)	466 (73.2)	137 (76.6)	61 (78.1)	49 (79.3)	53 (80.6)	81 (82.6)	114 (85.4)	592 (100.0)	0.25	>32
E. aerogenes (1,460)	8 (0.5)	50 (4.0)	498 (38.1)	417 (66.6)	96 (73.2)	55 (77.0)	26 (78.8)	17 (79.9)	19 (81.2)	26 (83.0)	45 (86.1)	94 (92.5)	109 (100.0)	0.12	32
M. morganii (1,205)	11 (0.9)	103 (9.5)	325 (36.4)	239 (56.3)	106 (65.1)	73 (71.1)	45 (74.9)	35 (77.8)	29 (80.2)	28 (82.5)	36 (85.5)	27 (87.7)	148 (100.0)	0.12	>32
C. koseri (866)	4 (0.5)	25(3.3)	288 (36.6)	397 (82.4)	56 (88.9)	64 (96.3)	18 (98.4)	3 (98.7)	2 (99.0)	1 (99.1)	1 (99.2)	3 (99.5)	4 (100.0)	0.12	0.5
C. freundii (1,051)	1 (0.1)	5 (0.6)	37 (4.1)	302 (32.8)	353 (66.4)	98 (75.7)	21 (77.7)	9 (78.6)	11 (79.6)	11 (80.7)	25 (83.1)	36 (86.5)	142 (100.0)	0.25	>32
S. marcescens (2,020)				7 (0.3)	128 (6.7)	687 (40.7)	776 (79.1)	201 (89.1)	68 (92.4)	55 (95.1)	31 (96.7)	28 (98.1)	39 (100.0)	1	4
Proteus vulgaris (567)		6 (1.1)	8 (2.5)	18 (5.6)	76 (19.0)	101 (36.9)	92 (53.1)	49 (61.7)	39 (68.6)	33 (74.4)	39 (81.3)	37 (87.8)	69 (100.0)	1	>32
Providencia spp. (917)	5 (0.5)	111 (12.6)	178 (32.1)	90 (41.9)	57 (48.1)	83 (57.1)	117 (69.9)	77 (78.3)	61 (85.0)	40 (89.3)	42 (93.9)	14 (95.4)	42 (100.0)	0.5	16
H. influenzae (4,414)	3865 (87.6)	427 (97.2)	94 (99.4)	20 (99.8)	6 (>99.9)	1 (>99.9)	1 (100.0)							≤0.015	0.03
β-lactamase-negative (3,267)	3045 (93.2)	200 (99.3)	19 (99.9)	3 (100.0)										≤0.015	≤0.015
β-lactamase-positive (1,147)	820 (71.5)	227 (91.3)	75 (97.8)	17 (99.3)	6 (99.8)	1 (99.9)	1 (100.0)							≤0.015	0.03
H. parainfluenzae (428)	375 (87.6)	30 (94.6)	8 (96.5)	8 (98.4)	2 (98.8)	2 (99.3)	2 (99.8)	1 (100.0)						≤0.015	0.03
M. catarrhalis (1,929)	293 (15.2)	509 (41.6)	614 (73.4)	381 (93.2)	119 (99.3)	12 (99.9)	1 (100.0)							0.06	0.12

Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; PEN = penicillin; S = susceptible; I = intermediate; R = resistant; CRO = ceftriaxone; NS = non-susceptible; ESBL-phenotype = extended-spectrum β-lactamase positive screening according to CLSI criteria.

Figure 2. Yearly frequency of selected resistance phenotypes

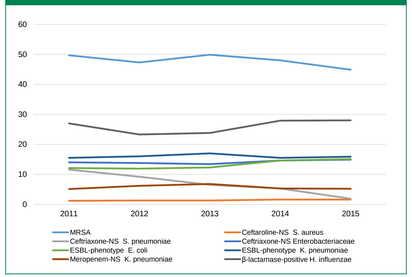
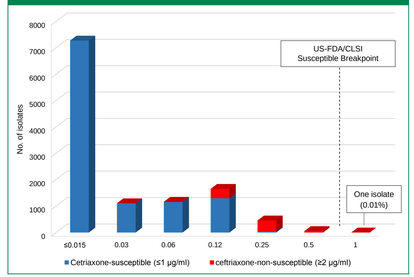


Figure 3. Ceftaroline activity against *S. pneumoniae* (n=11,696)



Conclusions

- Ceftaroline demonstrated potent and consistent (2011-2015) *in vitro* activity against staphylococci, including MRSA, different streptococcal groups, and *Haemophilus* spp.
- Ceftaroline also had an activity against Enterobacteriaceae most similar to that of currently available broad-spectrum cephalosporins.
- These results are similar to those of previous publications and indicate that ceftaroline *in vitro* activity against key bacterial species remained stable since its approval for clinical use in the USA in 2010.
- The results presented here coupled with documented efficacy of ceftaroline fosamil in the treatment of serious infections make this agent particularly attractive in the initial management of CABP and ABSSSI patients requiring hospitalization.

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