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Ceftaroline and Comparator Potency among Nine USA Census Regions: Report from the 2011 Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program

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Abstract

Background: Ceftaroline fosamil, prodrug of ceftaroline, is a broad spectrum cephalosporin approved by the USA-FDA for treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.

Methods: 11,676 isolates from 67 USA centers were cultured and tested for susceptibility to ceftaroline and comparators by reference CLSI MIC methods and results were analyzed by USA Census regions.

Results: *S. aureus*, including MRSA, and coagulase-negative staphylococci were particularly susceptible to ceftaroline (MIC_{90}, 1 and 0.5 µg/mL respectively). MRSA overall rate was 49.4%, varying from 36.7-38.7% (Mid-Atlantic [MAT], New England [NE]) to 55.0-56.5% (East [E] South Central [SC], West SC [WSC] and South Atlantic [SAT]). 96.7% (MAT) to 100.0% (3 regions) of *S. aureus* were susceptible to ceftaroline. Penicillin-resistant *S. pneumoniae* (≥2 µg/mL; 23.4% overall) varied from 17.1-17.2% (MAT, NE) to 34.6% (SAT), and β-lactamase production among *H. influenzae* (26.9% overall) ranged from 20.5 (WSC) to 32.7% (E North [N] Central). The highest rates of ESBL-phenotype *E. coli* (26.4%) and *Klebsiella* spp. (KSP; 29.8%) were observed in MAT. Meropenem-non-S KSP was ≤2.3% in 5 regions and highest in MAT (13.7%) and WSC (7.8%). Ceftazidime-non-susceptible *E. cloacae* (20.9% overall) ranged from 8.1 (W N Central) to 27.3% (MAT).

Conclusions: Regional differences in ceftaroline activity among staphylococci, streptococci, *Haemophilus* spp., and *M. catarrhalis* were minimal due to its high *in vitro* potency. Greater differences in ceftaroline activity were observed among the Enterobacteriaceae due to the greater diversity of organism types and resistance mechanisms, including production of ESBLs and KPC-producing strains.

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 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 newly released agent against relevant pathogens. We report the *in vitro* activity of ceftaroline against bacterial organisms isolated in USA medical centers in 2011 as part of the USA AWARE Program.

Methods

Organisms collection: A total of 11,676 bacterial isolates were collected through the AWARE program in 2011. Sixty-seven medical centers distributed across all nine USA Census Regions (4 to 10 medical centers per region) contributed clinical isolates. Organisms were consecutively collected from clinical infections and target numbers of strains for each of the requested bacterial species/genus were predetermined in the study protocol. The isolates were from respiratory tract infection (4,355; 37.3%), skin and skin structure infection (3,272; 28.0%), bloodstream infection (2,260; 19.4%), urinary tract infection (858; 7.3%) and other sites (931; 8.0%). 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-S22 and M45-A2 breakpoints, whereas ceftaroline interpretations were based on the breakpoint criteria established by the USA-FDA. *S. pneumoniae* were tested in Mueller-Hinton broth supplemented with 3-5% lysed horse blood, and *H. influenzae* were tested in Haemophilus Test Media, whereas *S. aureus* isolates were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains assured proper test conditions.

Results

- *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). MRSA overall rate was 49.4%, varying from 36.7-38.7% in the Mid-Atlantic and New England regions, to 55.0-56.5% in the East South Central, West South Central and South Atlantic regions (Figure 1)
- Ceftaroline inhibited 99.0% of *S. aureus* strains at the susceptible breakpoint of ≤1 µg/mL. Susceptibility rates to levofloxacin and clindamycin were 60.9 and 84.6%, respectively, according to CLSI breakpoints. Daptomycin, linezolid, tigecycline, and vancomycin showed 99.9-100.0% susceptibility (Table 2)
- Overall, 98.0% of MRSA strains were susceptible to ceftaroline ($MIC_{50/90}$, 0.5/1 µg/mL; highest MIC, 2 µg/mL; Table 1). MRSA susceptibility to ceftaroline varies from 96.7% in the Mid-Atlantic region to 100.0% in the East North Central, West North Central, and Pacific regions (data not shown).
- Ceftaroline inhibited 99.1% of *S. pneumoniae* at the MIC of ≤0.25 µg/mL and the highest MIC was only 0.5 µg/mL (Table 1 and 2 and Figure 2). Susceptibility to ceftriaxone (88.4% overall) varied from 91.9% in the Mountain region to 82.7% in the South Atlantic region, and susceptibility to penicillin (MIC, ≤2 µg/mL; 85.2% overall) varied from 89.4% in the Pacific region to 75.8% in the South Atlantic region (Figure 2)
- Ceftaroline was very potent against β-haemolytic streptococci ($MIC_{50/90}$, ≤0.015/0.03 µg/mL; highest MIC, 0.06 µg/mL) and viridans group streptococci ($MIC_{50/90}$, 0.03/0.12 µg/mL; Tables 1 and 2)
- Ceftaroline inhibited 99.6% of *H. influenzae* strains at MIC of 0.12 µg/mL or less, and the highest MIC value was only 0.5 µg/mL (Table 1)
- Ceftaroline activity against Enterobacteriaceae strains was similar to that of ceftriaxone (Table 2). Generally, non-ESBL phenotype strains were susceptible to ceftaroline, whereas ESBL-producing strains had elevated ceftaroline MIC values (Figure 3)
- ESBL rates among *E. coli* (12.1% overall) and *Klebsiella* spp. (15.4% overall) varied significantly among USA Census regions with highest rates observed in the Mid-Atlantic region (Figure 4)
- Meropenem-non-susceptible *Klebsiella* spp. represented ≤2.3% of the *Klebsiella* spp. Isolates in five regions and highest in the Mid-Atlantic (13.7%) and West South Central (7.8%) regions (Figure 4)
- Ceftazidime-non-susceptible *E. cloacae* (20.9% overall) ranged from 8.1% in the West North Central region to 27.3% in the Mid-Atlantic region (data not shown).

Table 1. Summary of Ceftaroline Activity Against Bacterial Isolates from USA Medical Centers (2011)

	Cumulative % (all regions) inhibited at ceftaroline MIC (µg/mL) of:								
Organism (no. tested)	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4
Staphylococcus aureus (2169)	-	0.1	0.4	9.1	50.6	83.4	99.0	100.0	-
MSSA (1098)	-	0.1	0.7	17.8	97.4	100.0	-	-	-
MRSA (1071)	-	-	-	0.3	2.7	66.3	98.0	100.0	-
Streptococcus pneumoniae (2149)	59.0	67.8	76.5	92.3	99.1	100.0	-	-	-
Penicillin-resistant (≥2 µg/mL; 502)	-	0.4	5.8	67.1	96.0	100.0	-	-	-
Ceftriaxone-non-susceptible (≥2 µg/mL; 249)	-	0.4	1.2	38.6	92.4	100.0	-	-	-
β-haemolytic streptococci (1144)	88.8	99.8	100.0	-	-	-	-	-	-
Coag.-negative staphylococci (645)	0.8	2.8	25.9	41.7	74.6	97.5	99.7	100.0	-
Viridans group streptococci (560)	47.9	77.1	88.4	94.6	97.1	98.9	100.0	-	-
Haemophilus influenzae (909)	82.4	95.4	98.6	99.6	99.9	100.0	-	-	-
Moraxella catarrhalis (294)	14.0	44.2	73.8	93.9	98.6	99.7	100.0	-	-
Escherichia coli (726)	0.8	9.6	43.3	67.9	78.9	83.1	85.7	87.5	88.0
Klebsiella spp. (1063)	0.4	3.8	35.8	60.7	74.2	81.6	84.4	85.0	86.1

Table 2. Activity of Ceftaroline and Comparator Antimicrobial Agents When Tested Against Bacterial Isolates from USA Medical Centers (2011)

Antimicrobial agent (no. tested)	MIC (µg/mL)			%S / %I / %R	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Staphylococcus aureus (2,169)					
Ceftaroline[b]	0.25	1	0.03 – 2	99.0 / - / -	- / - / -
Ceftriaxone	8	>8	1 – >8	50.6 / 0.0 / 49.4	50.6 / 0.0 / 49.4
Oxacillin	1	>2	≤0.25 – >2	50.6 / 0.0 / 49.4	50.6 / 0.0 / 49.4
Clindamycin	≤0.25	>2	≤0.25 – >2	84.6 / <0.1 / 15.3	84.5 / 0.1 / 15.4
Levofloxacin	0.25	>4	≤0.12 – >4	60.9 / 2.2 / 36.9	60.9 / 2.2 / 36.9
Tigecycline[c]	0.06	0.12	≤0.03 – 0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	1	2	0.25 – 8	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
Vancomycin	1	1	0.25 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / - / -	100.0 / 0.0 / 0.0
β-haemolytic streptococci (1,144)					
Ceftaroline[b]	≤0.015	0.03	≤0.015 – 0.06	- / - / -	- / - / -
Ceftriaxone	≤0.06	0.12	≤0.06 – 1	99.9 / - / -	100.0 / 0.0 / 0.0
Penicillin	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	81.9 / 0.2 / 17.9	82.1 / 0.0 / 17.9
Levofloxacin	0.5	1	≤0.12 – >4	99.5 / 0.1 / 0.4	95.0 / 4.5 / 0.5
Tigecycline[c]	≤0.03	≤0.03	≤0.03 – 0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	1	1	≤0.12 – 2	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Streptococcus pneumoniae (2,149)					
Ceftaroline[b]	≤0.015	0.12	≤0.015 – 0.5	99.1 / - / -	- / - / -
Ceftriaxone	≤0.06	2	≤0.06 – 8	88.4 / 10.3 / 1.3	76.1 / 22.6 / 1.3
Penicillin[d]	≤0.06	4	≤0.06 – 8	85.2 / 12.8 / 1.9	- / -
Penicillin[e]	≤0.06	4	≤0.06 – 8	56.3 / 20.3 / 23.4	56.3 / 28.9 / 14.8
Amoxicillin/clavulanate	≤1	8	≤1 – >8	81.1 / 4.8 / 14.1	- / - / -
Erythromycin	≤0.12	>16	≤0.12 – >16	55.2 / 0.4 / 44.4	55.2 / 0.4 / 44.4
Clindamycin	≤0.25	>2	≤0.25 – >2	78.2 / 0.6 / 21.2	78.8 / 0.0 / 21.2
Levofloxacin	1	1	≤0.12 – >4	98.7 / <0.1 / 1.2	98.7 / 0.0 / 1.3
Haemophilus influenzae (909)					
Ceftaroline[b]	≤0.015	0.03	≤0.015 – 0.5	99.6 / - / -	- / - / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Ampicillin	0.25	>8	≤0.12 – >8	72.4 / 1.2 / 26.4	72.4 / 0.0 / 27.6
Amoxicillin/clavulanate	≤1	≤1	≤1 – 8	99.9 / 0.0 / 0.1	90.2 / 0.0 / 9.8
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5 – 2	99.9 / 0.0 / 0.1	- / - / -
Tigecycline[c]	0.25	0.5	0.03 – 2	- / - / -	- / - / -
Azithromycin	1	2	≤0.03 – >4	98.9 / - / -	1.2 / 97.7 / 1.1
Levofloxacin	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Moraxella catarrhalis (294)					
Ceftaroline[b]	0.06	0.12	≤0.015 – 1	- / - / -	- / - / -
Ceftriaxone	0.25	0.5	≤0.06 – 2	100.0 / - / -	99.3 / 0.7 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tetracycline	0.25	0.25	≤0.12 – 1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
TMP/SMX[f]	≤0.5	≤0.5	≤0.5 – 4	96.6 / 3.1 / 0.3	96.6 / 2.4 / 1.0
Levofloxacin	≤0.12	≤0.12	≤0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Escherichia coli (726)					
Ceftaroline[b]	0.12	32	≤0.015 – >32	83.1 / 2.6 / 14.3	- / - / -
Ceftriaxone	≤0.06	>8	≤0.06 – >8	89.1 / 0.3 / 10.6	89.1 / 0.3 / 10.6
Ampicillin/sulbactam	8	>32	≤0.25 – >32	50.1 / 23.8 / 26.1	- / - / 49.9
Piperacillin/tazobactam	2	8	≤0.5 – >64	93.8 / 1.9 / 4.3	91.7 / 2.1 / 6.2
Tigecycline[c]	0.12	0.12	≤0.03 – 1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Gentamicin	≤1	>8	≤1 – >8	87.3 / 0.6 / 12.1	86.5 / 0.8 / 12.7
Levofloxacin	≤0.12	>4	≤0.12 – >4	69.6 / 0.5 / 29.9	69.3 / 0.3 / 30.4
Meropenem	≤0.06	≤0.06	≤0.06 – 1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Klebsiella spp.[g] (1,063)					
Ceftaroline[b]	0.12	>32	≤0.015 – >32	81.6 / 2.8 / 15.6	- / - / -
Ceftriaxone	≤0.06	>8	≤0.06 – >8	85.5 / 0.9 / 13.6	85.5 / 0.9 / 13.6
Ceftazidime	0.12	16	≤0.015 – >32	88.0 / 0.5 / 11.5	86.3 / 1.7 / 12.0
Ampicillin/sulbactam	8	>32	0.5 – >32	70.5 / 11.0 / 18.5	- / - / 29.5
Piperacillin/tazobactam	2	>64	≤0.5 – >64	88.0 / 1.6 / 10.4	82.4 / 5.6 / 12.0
Tigecycline[c]	0.25	1	0.06 – >4	98.5 / 1.3 / 0.2	94.6 / 3.9 / 1.5
Gentamicin	≤1	2	≤1 – >8	92.8 / 1.7 / 5.5	91.7 / 1.1 / 7.2
Levofloxacin	≤0.12	>4	≤0.12 – >4	88.4 / 1.1 / 10.5	87.4 / 1.0 / 11.6
Meropenem	≤0.06	≤0.06	≤0.06 – >8	96.0 / 0.1 / 3.9	96.1 / 0.7 / 3.2
Enterobacter cloacae (383)					
Ceftaroline[b]	0.25	>32	≤0.015 – >32	- / - / -	- / - / -
Ceftriaxone	0.25	>8	≤0.06 – >8	75.2 / 1.6 / 23.2	75.2 / 1.6 / 23.2
Ceftazidime	0.25	>32	0.03 – >32	79.1 / 1.3 / 19.6	76.0 / 3.1 / 20.9
Ampicillin/sulbactam	16	>32	1 – >32	34.5 / 21.9 / 43.6	- / - / 65.5
Piperacillin/tazobactam	2	64	≤0.5 – >64	83.0 / 8.6 / 8.4	80.4 / 2.6 / 17.0
Tigecycline[c]	0.25	0.5	0.12 – 4	98.4 / 1.6 / 0.0	96.1 / 2.3 / 1.6
Gentamicin	≤1	≤1	≤1 – >8	94.2 / 0.8 / 5.0	93.7 / 0.5 / 5.8
Levofloxacin	≤0.12	0.5	≤0.12 – >4	93.2 / 1.6 / 5.2	92.7 / 0.5 / 6.8
Meropenem	≤0.06	≤0.06	≤0.06 – >8	98.2 / 0.5 / 1.3	98.7 / 1.0 / 0.3

a. Criteria as published by the CLSI [2012] and EUCAST [2012]. β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied when available [Teflaro Product Insert, 2012].
c. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2011].
d. Criteria as published by the CLSI [2012] for 'Penicillin parenteral (non-meningitis)'.
e. Criteria as published by the CLSI [2012] for 'Penicillin (oral penicillin V)'.
f. Trimethoprim/sulfamethoxazole.
g. Includes: *Klebsiella oxytoca* (245 strains) and *K. pneumoniae* (818 strains).

Figure 1. Susceptibility of *S. aureus* (n=2,169) to Ceftaroline (MIC, ≤1 µg/mL) and MRSA Rates by USA Census Region (2011)

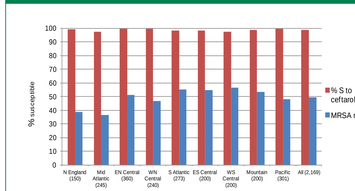


Figure 2. Susceptibility of *S. pneumoniae* (n=2,149) to Ceftaroline (MIC, ≤0.25 µg/mL), Ceftriaxone (MIC, ≤1 µg/mL), and Penicillin (MIC, ≤2 µg/mL) by USA Census Region (2011)

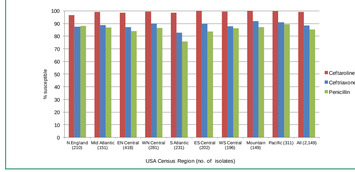


Figure 3. MIC Distributions for Ceftaroline and 1,789 USA Clinical Isolates of ESBL (n=252) and non-ESBL (n=1,537) Enterobacteriaceae from USA Medical Centers in 2011. The Collection Includes *E. coli* (726), *K. pneumoniae* (818), and *K. oxytoca* (245)

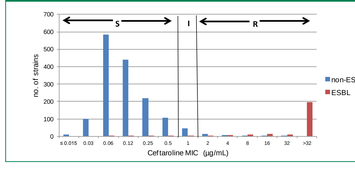
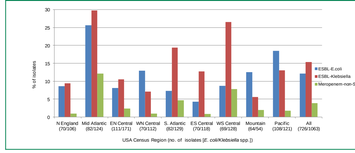


Figure 4. ESBL Rates among *E. coli* and *Klebsiella* spp. and Meropenem-non-susceptibility Rates among *Klebsiella* spp. by USA Census Region



Conclusions

- Regional differences in ceftaroline activity among staphylococci, streptococci, *Haemophilus* spp., and *M. catarrhalis* were minimal due to its high *in vitro* potency.
- Greater differences in ceftaroline activity were observed among the Enterobacteriaceae due to the diversity of organism types and resistance mechanisms, including production of ESBLs and the occurrence KPC-producing strains.

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