Antimicrobial Susceptibility Trends among *Staphylococcus aureus* from US Hospitals: Results from 7 Years of the Ceftaroline (AWARE) Surveillance Program (2009-2015)

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ABSTRACT

Background: Ceftaroline (CPT) is a broad-spectrum cephalosporin with *in vitro* activity against *Staphylococcus aureus* (SA), including methicillin-resistant SA (MRSA), multidrug-resistant *Streptococcus pneumoniae,* and wild-type (ie, non-ESBL-producing) *Enterobacteriaceae.* The prodrug CPT fosamil was approved for clinical use in the United States (US) in October 2010, and the AWARE Program monitors the *in vitro* activity of CPT against clinical bacteria from various infection types. We evaluated trends in SA susceptibility (S) rates to CPT and comparators in the 2009-2015 period.

Methods: Clinically significant bacterial isolates were consecutively collected (1/patient) from various infection types and all SA (n=19,036) from medical centers that participated in the AWARE Program during the entire period (n=42; from 30 states in 9 Census divisions) were evaluated. Susceptibility to CPT and comparator agents was performed by CLSI broth microdilution methods. Chi-square for trend test was performed with the EpiInfo™ 7.

Results: Isolates were mainly from skin/soft tissue (50.8%), respiratory tract (21.7%), and bloodstream (20.0%) infections. MRSA rates varied from 47.2% in 2009 to a low of 43.6% in 2015 (46.8% overall). CPT inhibited all SA strains at ≤2 µg/mL and CPT-S rates remained stable during the study period, varying from 98.6% in 2009 to 98.7% in 2015. CPT was very active against MRSA ($MIC_{50/90}$, 0.5/1 µg/mL), with S rates varying from 97.1% in 2009 to 97.0% in 2015 (highest of 98.8% in 2010 and lowest of 95.6% in 2014). Daptomycin, linezolid, tigecycline, vancomycin (all with ≥99.9%S overall), and trimethoprim-sulfamethoxazole (97.8%S) were also very active against MRSA with no marked variation during the study period. In contrast, MRSA S to clindamycin (MIC ≤0.5 µg/mL) increased from 64.4% in 2009 to 71.8% in 2015 (72.7% overall and highest of 74.8% in 2012). Against methicillin-S SA (MSSA), CPT ($MIC_{50/90}$, 0.25/0.25 µg/mL) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 µg/mL). MSSA S rates remained stable for clindamycin (94.5%/94.9% in 2009/2015), levofloxacin (89.4%/89.1% in 2009/2015), and tetracycline (95.3%/96.7% in 2010/2015), but decreased for erythromycin (68.6%/64.4% in 2009/2015).

Conclusions: The results of this investigation indicate that MRSA rates decreased in the 2009-2015 period in US hospitals participating in the AWARE program. CPT retained potent *in vitro* activity against MRSA and MSSA with no marked variations or trends (MIC creep) during the study period.

INTRODUCTION

- Ceftaroline fosamil (Teflaro®), prodrug of ceftaroline, was approved in 2010 by the United States (US) 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*
- The antimicrobial resistance surveillance program Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) Program was designed to monitor the activity of ceftaroline and comparator agents and provides contemporary and longitudinal information on the activity of this agent against relevant pathogens
- We evaluated trends in *S. aureus* susceptibility rates to ceftaroline and comparators in the 2009-2015 period

MATERIALS AND METHODS

Organism Collection

- Clinically significant bacterial isolates were consecutively collected (1/patient) from various infection types
- All *S. aureus* (n=19,036) from medical centers that participated in the AWARE Program during the entire period (2009-2015) were evaluated
- Isolates were from 42 medical centers in 30 states from all 9 census divisions; all medical centers participated in the AWARE Program during the entire period of this investigation (2009-2015)

Susceptibility Testing Methods

- Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) methods were performed to determine antimicrobial susceptibility of ceftaroline and selected comparator antimicrobials
- MIC panels were manufactured by JMI Laboratories in 2015 and by ThermoFisher Scientific (Cleveland, Ohio, USA) in 2009-2014
- MIC results were interpreted per CLSI and EUCAST breakpoint criteria. A susceptible breakpoint of ≤1 µg/mL was applied for ceftaroline as indicated by CLSI and EUCAST and based on ceftaroline fosamil 600 mg q12h dosage
- Chi-square test for trend was performed with the EpiInfo™ 7

Table 1 Activity of ceftaroline and comparator antimicrobial agents when tested against 19,036 *S. aureus* (2009–2015)

Organism / antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
S. aureus (19,036)						
Ceftaroline	0.25	1	98.7	0.0	98.7	1.3
Ceftriaxone	4	>8	53.2	46.8		
Oxacillin	1	>2	53.2	46.8	53.2	46.8
Erythromycin	>4	>4	40.2	56.7	40.6	58.2
Clindamycin	≤0.25	>2	84.5	15.3	84.1	15.5
Levofloxacin	≤0.5	>4	62.8	36.0	62.8	36.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	98.7	1.3	98.7	1.3
Tetracycline	≤0.5	≤0.5	95.3	4.1	93.6	5.5
Tigecycline	0.06	0.12	>99.9[b]		>99.9	<0.1
Linezolid	1	1	>99.9	<0.1	>99.9	<0.1
Vancomycin	1	1	>99.9	0.0	>99.9	<0.1
Daptomycin	0.25	0.5	99.9		99.9	0.1
MSSA (10,134)						
Ceftaroline	0.25	0.25	100.0	0.0	100.0	0.0
Ceftriaxone	4	4	100.0	0.0		
Erythromycin	≤0.25	>4	65.9	29.3	66.4	31.9
Clindamycin	≤0.25	≤0.25	94.8	5.0	94.4	5.2
Levofloxacin	≤0.5	4	89.1	10.1	89.1	10.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	99.4	0.6	99.4	0.6
Tetracycline	≤0.5	≤0.5	96.0	3.3	94.8	4.9
Tigecycline	0.06	0.12	100.0[b]		100.0	0.0
Linezolid	1	1	>99.9	<0.1	>99.9	<0.1
Vancomycin	1	1	100.0	0.0	100.0	0.0
Daptomycin	0.25	0.5	>99.9		>99.9	<0.1
MRSA (8,902)						
Ceftaroline	0.5	1	97.3	0.0	97.3	2.7
Erythromycin	>4	>4	11.0	86.6	11.3	88.1
Clindamycin	≤0.25	>2	72.7	27.1	72.4	27.3
Levofloxacin	4	>4	32.7	65.5	32.7	65.5
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	97.8	2.2	97.8	2.2
Tetracycline	≤0.5	1	94.4	5.0	92.3	6.1
Tigecycline	0.06	0.12	>99.9[b]		>99.9	<0.1
Linezolid	1	1	>99.9	<0.1	>99.9	<0.1
Vancomycin	1	1	>99.9	0.0	>99.9	<0.1
Daptomycin	0.25	0.5	99.9		99.9	0.1

[a] Criteria as published by CLSI [2017] and EUCAST [2017]
[b] Breakpoints from FDA Package Insert

RESULTS

- Isolates were mainly from skin and skin structure (50.8%), respiratory tract (21.7%), and bloodstream (20.0%) infections (Figure 1)
- Ceftaroline inhibited all *S. aureus* strains at ≤2 µg/mL and ceftaroline susceptibility rates remained stable during the study period, varying from 98.6% in 2009 to 98.7% in 2015 (Figures 2 to 5)
- MRSA rates decreased from 47.2% in 2009 to a low of 43.6% in 2015 ($p<0.01$; 46.8% overall; Figure 4)
- Ceftaroline was very active against MRSA ($MIC_{50/90}$, 0.5/1 µg/mL) with susceptibility rates varying from 97.1% in 2009 to 97.0% in 2015. The highest susceptibility rate (98.8%) was observed in 2010 and the lowest (95.6%) in 2014 (Figures 3 and 5)
- Daptomycin, linezolid, tigecycline, vancomycin (all with ≥99.9% susceptibility overall), and trimethoprim-sulfamethoxazole (97.8% susceptible) were also very active against MRSA with no marked variation during the study period (Table 1)
- MRSA susceptibility to clindamycin (CLSI breakpoint of ≤0.5 µg/mL) increased from 64.4% in 2009 to 73.2% in 2010 and remained relatively stable in the following years, ranging from a high of 74.8% in 2012 to a low of 71.8% in 2015 (72.7% overall; Table 1 and Figure 5)
- When tested against MSSA, ceftaroline ($MIC_{50/90}$, 0.25/0.25 µg/mL) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 µg/mL; Table 1)
- MSSA susceptibility rates remained stable for clindamycin (94.5%/94.9% in 2009/2015), levofloxacin (89.4%/89.1% in 2009/2015), and tetracycline (95.3%/96.7% in 2010/2015), but decreased for erythromycin (68.6%/64.4% in 2009/2015; data not shown)
- Overall, EUCAST and CLSI categorical interpretations showed good agreement for tested drugs

Figure 1 Distribution of organisms by infection type

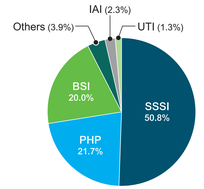


Figure 2 Ceftaroline activity (MIC distributions) against MSSA isolates from US medical centers stratified by year (n = 10,134; 2009-2015)

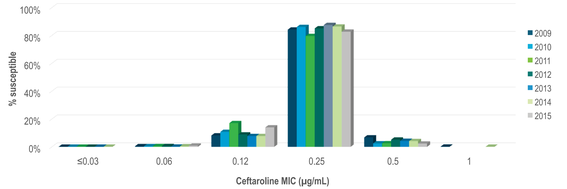


Figure 3 Ceftaroline activity (MIC distributions) against MRSA isolates from US medical centers stratified by year (n = 8,902; 2009-2015)

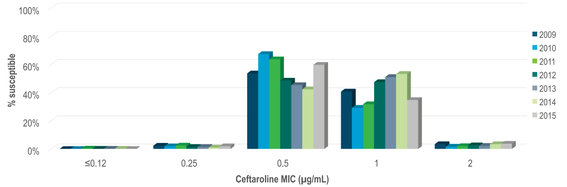


Figure 4 *S. aureus* antimicrobial susceptibility stratified by year (2009-2015)

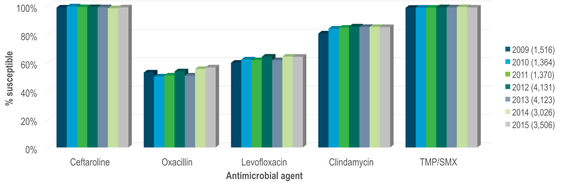
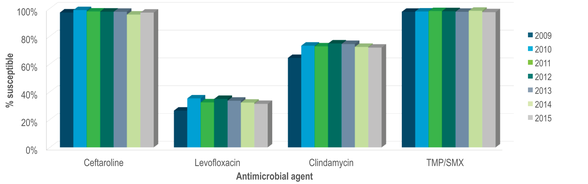


Figure 5 MRSA antimicrobial susceptibility of MRSA stratified by year (2009-2015)



CONCLUSIONS

- The results of this investigation indicate that MRSA rates decreased in the 2009-2015 period in US hospitals participating in the AWARE program
- Ceftaroline retained potent *in vitro* activity against MRSA and MSSA with no marked variations or trends (MIC creep) during the study period

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