

Comparison of *In vitro* Activity of Ceftaroline Against *Staphylococcus aureus* from In- and Out-Patients from the AWARE Surveillance Program, 2014 - 2015

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Abstract

Background: Ceftaroline, the active metabolite of ceftaroline-fosamil, is a cephalosporin developed for treating infections caused by *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), *Streptococcus pneumoniae*, β -hemolytic streptococci, and some gram-negative pathogens. The analysis reported here was done to evaluate what differences might exist for ceftaroline *in vitro* activity against MRSA and methicillin-susceptible *S. aureus* (MSSA) collected from in- and out-patients in 2014 -2015 globally. **Methods:** 19,700 *S. aureus* (11,750 MRSA and 7,950 MSSA), were collected worldwide during 2014 - 2015 from in-patients (IP) (n=17,578) and out-patients (OP) (n=2,122). IP isolates were collected from patients in ICU or medical wards; OP isolates were collected from patients in the Emergency Room. Isolates were from (IP/OP): complicated skin and skin structure (55.1%/68.1%), lower respiratory tract (28.6%/11.6%), blood (8.0%/11.2%), complicated intraabdominal (4.4%/2.0%), complicated urinary tract (3.7%/6.1%), and other (<1%/<1%) infection sources, and from all ages (0-17 years, IP 11.0%, OP 10.2%; >17 years, IP 88.5%, OP 89.3; age unknown, 0.5% IP and OP). MIC values were determined by broth microdilution according to CLSI guidelines and percent susceptibility (%S) interpreted using the EUCAST breakpoint (≤ 1 mg/L susceptible). **Results:** Ceftaroline activity based on %S is shown in the table. All MSSA isolates were ceftaroline susceptible (MIC range 0.015-0.5 mg/L, MIC_{50/90} 0.25/0.25 mg/L) while 91.4% of MRSA were ceftaroline susceptible (MIC range 0.03-8 mg/L, MIC_{50/90} 0.5/1 mg/L).

Organism	Location	%S to ceftaroline (n)					
		Global	Europe	LA	NA	ME/Af	Asia/SP
MRSA	IP	91.0	94.4	84.8	99.4	92.0	79.8
		(10,522)	(4,993)	(1,422)	(1,414)	(846)	(1,847)
		94.4	96.8	90.7	100	97.1	88.4
MRSA	OP	(1,228)	(469)	(378)	(167)	(68)	(146)
		100	100	100	100	100	100
		(7,056)	(3,630)	(1,120)	(683)	(558)	(1,065)
MSSA	IP	100	100	100	100	100	100
		(894)	(320)	(284)	(87)	(79)	(124)
		100	100	100	100	100	100
MSSA	OP	(894)	(320)	(284)	(87)	(79)	(124)
		100	100	100	100	100	100
		(894)	(320)	(284)	(87)	(79)	(124)

LA, Latin America; NA, North America; ME/Af, Middle East/Africa; SP, South Pacific

Conclusions: Ceftaroline was highly active *in vitro* against MSSA worldwide, with 100% susceptible. Globally, 91.0% of IP MRSA and 94.4% of OP MRSA were susceptible. Differences in percent susceptible may reflect the higher proportion of isolates from respiratory sources in the IP group. Activity was slightly reduced in IP MRSA from LA, and IP and OP MRSA from Asia/SP. These findings suggest that the continued monitoring of ceftaroline activity should include tracking potential differences between MRSA encountered in the community and those that are healthcare associated.

Introduction

Ceftaroline, the active metabolite of ceftaroline-fosamil, is a cephalosporin developed for treating infections caused by *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), *Streptococcus pneumoniae*, β -hemolytic streptococci, and some gram-negative pathogens. This analysis evaluates ceftaroline's *in vitro* activity against MRSA and methicillin-susceptible *S. aureus* (MSSA) collected from in- and out-patients in 2014 - 2015 globally.

Materials & Methods

- A total of 19,700 *S. aureus* isolates were collected from in-patients (IP) (7,056 MSSA, 10,522 MRSA) and out-patients (OP) (894 MSSA, 1,228 MRSA) globally.
- Confirmation of isolate identification using MALDI-TOF mass spectroscopy and antibiotic susceptibility testing was performed at a central laboratory (IHMA, Inc., Schaumburg, IL).
- Broth microdilution antimicrobial susceptibility testing was performed following CLSI guidelines [1]. EUCAST interpretive guidelines were applied to define susceptibility [2] except where noted [3].

Results

Table 1. *In Vitro* Activity of Ceftaroline and Comparator Agents Tested Against *S. aureus* from in-patients and out-patients globally and by region, 2014 - 2015.

Organism	Antimicrobial	Global				Asia/South Pacific				Europe				Latin America				MidEast/Africa				North America			
		N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range
MRSA, IP	Ceftaroline	10522	91.0	1	0.03 - 8	1847	79.8	2	0.12 - 8	4993	94.4	1	0.03 - 4	1422	84.8	2	0.25 - 4	846	92.0	1	0.25 - 2	1414	99.4	1	0.25 - 2
	Clindamycin	10522	60.1	>4	≤ 0.03 - >4	1847	50.6	>4	≤ 0.03 - >4	4993	64.2	>4	≤ 0.03 - >4	1422	47.3	>4	≤ 0.03 - >4	846	63.0	>4	≤ 0.03 - >4	1414	69.0	>4	≤ 0.03 - >4
	Daptomycin	10522	99.8	1	0.12 - >2	1847	99.8	1	0.25 - 2	4993	99.7	1	0.12 - >2	1422	99.8	1	0.12 - 2	846	100	1	0.12 - 1	1414	99.8	1	0.12 - >2
	Erythromycin	10522	32.4	>8	≤ 0.12 - >8	1847	33.6	>8	≤ 0.12 - >8	4993	37.1	>8	≤ 0.12 - >8	1422	31.2	>8	0.25 - >8	846	39.0	>8	≤ 0.12 - >8	1414	11.5	>8	≤ 0.12 - >8
	Gentamicin	10522	37.3	>32	≤ 0.06 - >32	1847	26.7	>32	≤ 0.06 - >32	4993	40.2	>32	≤ 0.06 - >32	1422	42.5	>32	≤ 0.06 - >32	846	31.9	>32	≤ 0.06 - >32	1414	38.9	≤ 2	≤ 0.06 - >32
	Levofloxacin	10522	30.5	>4	0.03 - >4	1847	42.0	>4	0.06 - >4	4993	23.5	>4	0.03 - >4	1422	42.5	>4	0.12 - >4	846	29.8	>4	0.12 - >4	1414	28.8	>4	0.03 - >4
MRSA, OP	Linezolid	10522	100	2	≤ 0.5 - 4	1847	100	2	≤ 0.5 - 4	4993	100	2	≤ 0.5 - 4	1422	100	2	1 - 4	846	100	2	≤ 0.5 - 4	1414	100	2	≤ 0.5 - 4
	Trimethoprim Sulfamethoxazole	10522	95.4	≤ 1	≤ 0.25 - >4	1847	89.0	>4	≤ 0.25 - >4	4993	97.7	≤ 1	≤ 0.25 - >4	1422	98.3	≤ 1	≤ 0.25 - >4	846	89.6	>4	≤ 0.25 - >4	1414	96.0	≤ 1	≤ 0.25 - >4
	Vancomycin	10522	100	2	≤ 0.25 - 4	1847	99.9	2	≤ 0.25 - 4	4993	100	2	≤ 0.25 - 4	1422	100	2	≤ 0.25 - 2	846	100	2	≤ 0.25 - 2	1414	99.9	2	0.5 - 4
	Ceftaroline	1228	94.4	1	0.25 - 8	146	88.4	2	0.25 - 8	469	96.8	1	0.25 - 4	378	90.7	1	0.25 - 2	68	97.1	1	0.25 - 2	167	100	1	0.25 - 1
	Clindamycin	1228	73.9	>4	≤ 0.03 - >4	146	67.1	>4	0.06 - >4	469	76.6	>4	≤ 0.03 - >4	378	64.8	>4	≤ 0.03 - >4	68	85.3	>2	0.06 - >4	167	88.6	>2	≤ 0.03 - >4
	Daptomycin	1228	99.8	1	0.25 - 2	146	100	1	0.25 - 1	469	99.6	1	0.25 - 1	378	100	1	0.25 - 1	68	100	1	0.25 - 1	167	100	1	0.5 - 1
MSSA, IP	Erythromycin	1228	42.8	>8	≤ 0.12 - >8	146	48.6	>8	0.25 - >8	469	46.9	>8	≤ 0.12 - >8	378	42.3	>8	≤ 0.12 - >8	68	66.2	>8	0.25 - >8	167	18.0	>8	≤ 0.12 - >8
	Gentamicin	1228	43.1	32	≤ 0.06 - >32	146	41.1	>32	0.12 - >32	469	45.6	≤ 2	≤ 0.06 - >32	378	41.8	>32	0.12 - >32	68	36.8	>32	≤ 0.06 - >32	167	43.1	≤ 2	0.12 - >32
	Levofloxacin	1228	51.9	>4	0.06 - >4	146	58.9	>4	0.12 - >4	469	38.4	>4	0.06 - >4	378	62.2	>4	0.12 - >4	68	64.7	>4	0.12 - >4	167	55.1	>4	0.12 - >4
	Linezolid	1228	100	2	≤ 0.5 - 4	146	100	2	1 - 4	469	100	2	1 - 4	378	100	2	≤ 0.5 - 4	68	100	2	1 - 4	167	100	2	1 - 4
	Trimethoprim Sulfamethoxazole	1228	95.5	≤ 1	≤ 0.25 - >4	146	90.0	2	≤ 0.25 - >4	469	96.8	≤ 1	≤ 0.25 - >4	378	98.4	≤ 1	≤ 0.25 - >4	68	82.4	>4	≤ 0.25 - >4	167	95.2	≤ 1	≤ 0.25 - >4
	Vancomycin	1228	99.9	2	0.5 - 4	146	100	2	0.5 - 2	469	99.8	2	0.5 - 4	378	100	2	0.5 - 2	68	100	2	0.5 - 2	167	100	2	0.5 - 2
MSSA, OP	Ceftaroline	7056	100	0.25	≤ 0.015 - 0.5	1065	100	0.25	≤ 0.015 - 0.5	3630	100	0.25	≤ 0.015 - 0.5	1120	100	0.25	0.06 - 0.5	558	100	0.25	0.06 - 0.5	683	100	0.25	≤ 0.015 - 0.5
	Clindamycin	7056	96.2	0.12	≤ 0.03 - >4	1065	93.9	0.12	≤ 0.03 - >4	3630	96.9	0.12	≤ 0.03 - >4	1120	97.1	0.12	≤ 0.03 - >4	558	97.7	0.12	≤ 0.03 - >4	683	93.0	0.12	≤ 0.03 - >4
	Daptomycin	7056	99.9	1	≤ 0.06 - >2	1065	99.9	1	0.12 - 2	3630	99.9	1	≤ 0.06 - 2	1120	100	1	≤ 0.06 - 1	558	100	1	0.25 - 1	683	99.4	1	0.12 - >2
	Erythromycin	7056	81.3	>4	≤ 0.12 - >8	1065	85.2	>4	≤ 0.12 - >8	3630	84.9	>4	≤ 0.12 - >8	1120	78.8	>8	≤ 0.12 - >8	558	81.7	8	≤ 0.12 - >8	683	59.7	8	≤ 0.12 - >8
	Gentamicin	7056	43.9	≤ 2	≤ 0.06 - >32	1065	45.9	≤ 2	≤ 0.06 - >32	3630	41.9	≤ 2	≤ 0.06 - >32	1120	52.3	≤ 2	≤ 0.06 - >32	558	39.6	≤ 2	≤ 0.06 - >32	683	41.4	≤ 2	≤ 0.06 - >32
	Levofloxacin	7056	94.0	0.5	≤ 0.015 - >4	1065	95.4	0.5	0.06 - >4	3630	94.5	0.5	≤ 0.015 - >4	1120	97.1	0.25	≤ 0.015 - >4	558	90.7	1	0.06 - >4	683	86.7	>2	0.03 - >4
MSSA, OP	Linezolid	7056	100	2	≤ 0.5 - 4	1065	100	2	1 - 4	3630	100	2	≤ 0.5 - 4	1120	100	2	1 - 4	558	100	2	1 - 4	683	100	2	≤ 0.5 - 4
	Trimethoprim Sulfamethoxazole	7056	98.6	≤ 1	≤ 0.25 - >4	1065	98.4	≤ 1	≤ 0.25 - >4	3630	98.9	≤ 1	≤ 0.25 - >4	1120	99.3	≤ 1	≤ 0.25 - >4	558	95.2	1	≤ 0.25 - >4	683	98.5	≤ 1	≤ 0.25 - >4
	Vancomycin	7056	100	2	≤ 0.25 - 4	1065	100	2	≤ 0.25 - 2	3630	100	2	≤ 0.25 - 2	1120	100	2	≤ 0.25 - 2	558	100	2	0.5 - 2	683	100	2	≤ 0.25 - 2
	Ceftaroline	894	100	0.25	≤ 0.015 - 0.5	124	100	0.25	0.06 - 0.5	320	100	0.25	≤ 0.015 - 0.5	284	100	0.25	0.06 - 0.5	79	100	0.25	0.12 - 0.5	87	100	0.25	0.12 - 0.5
	Clindamycin	894	94.6	0.12	≤ 0.03 - >4	124	97.6	0.12	≤ 0.03 - >4	320	94.4	0.12	≤ 0.03 - >4	284	95.1	0.12	≤ 0.03 - >4	79	92.4	0.25	0.06 - >4	87	92.0	0.12	0.06 - >4
	Daptomycin	894	100	1	≤ 0.06 - 1	124	100	1	0.25 - 1	320	100	1	≤ 0.06 - 1	284	100	1	0.25 - 1	79	100	1	0.12 - 1	87	100	1	0.25 - 1
MSSA, OP	Erythromycin	894	77.2	>8	≤ 0.12 - >8	124	88.7	>4	≤ 0.12 - >8	320	79.1	>8	≤ 0.12 - >8	284											