

# Ceftaroline Activity Tested against Bacterial Isolates from Pediatric Patients: Results from the Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) Program for the United States (2011-2012)

HS SADER, RK FLAMM, RN JONES  
JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, MD, PhD  
JMI Laboratories  
North Liberty, IA, USA  
www.jmilabs.com  
ph. 319.665.3370  
fax 319.665.3371  
helio-sader@jmilabs.com

## Abstract

**Background:** Ceftaroline (CPT), the active form of CPT fosamil, is a cephalosporin with broad-spectrum bactericidal activity against resistant (R) gram-positive (GP) organisms, including methicillin-R *S. aureus* (MRSA), and many Enterobacteriaceae species. CPT fosamil is FDA-approved for treatment of acute bacterial skin/skin structure infections and community-acquired bacterial pneumonia in adults.

**Methods:** 5,291 consecutive unique pediatric patient strains of clinical significance were collected from 157 USA medical centers as part of the AWARE Program. The isolates were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) for reference antimicrobial susceptibility (S) testing. S results were analyzed according to patient age as follows:  $\leq 1$  years old (yo; 1,857 strains); 2-5 (1,342); 6-12 (1,281) and 13-17 (811).

**Results:** MRSA rates were slightly lower in isolates from patients 13-17 yo (39.9%) compared to other age groups, and CPT was consistently active against *S. aureus* (SA) isolates from all four age groups (MIC<sub>50/90</sub>: 0.25-0.5/1  $\mu$ g/mL; 99.8-100.0% S). 99.8% of MRSA were CPT-S (MIC<sub>50/90</sub>: 0.5/1  $\mu$ g/mL). R rates to erythromycin, clindamycin and levofloxacin among SA did not vary significantly among age groups. All *S. pneumoniae* (SPN) strains (1,178) were CPT-S (MIC<sub>50/90</sub>:  $\leq 0.015/0.12$   $\mu$ g/mL), while ceftriaxone S varied from 84.8 ( $\leq 1$  yo) to 89.7% (13-17 yo). The highest CPT MIC among *H. influenzae* (HI; 587 strains) was 0.12  $\mu$ g/mL (100.0% S), and  $\beta$ -lactamase production rates varied from 24.2 (13-17 yo) to 30.1% (6-12 yo); 27.9% overall. CPT was also very active against  $\beta$ -hemolytic streptococci (BHS; 556 strains, highest MIC 0.06  $\mu$ g/mL). ESBL-phenotype rates among *E. coli* (EC)/*Klebsiella* spp. (KSP) were 6.0/5.1, 11.0/11.5, 5.1/8.3 and 11.4/14.7% for the  $\leq 1$ , 2-5, 6-12 and 13-17 age groups, respectively. CPT exhibited good activity against non-ESBL-phenotype strains of EC and KSP (MIC<sub>90</sub>: 0.25  $\mu$ g/mL for both organisms), but limited activity against ESBL-producing strains.

**Conclusion:** CPT demonstrated potent in vitro activity against SA, SPN, BHS and HI isolated from pediatric patients, independent of patient age. Differences in S rates to comparator agents according to patient age group were observed mainly among EC and KSP.

Antimicrobial agent / organisms (no. tested)	% Susceptible by age group (years of age)				
	$\leq 1$	2-5	6-12	13-17	All ( $\leq 17$ )
<i>S. aureus</i> (633)	(493)	(527)	(464)	(2,117)	
Ceftaroline	99.8	100.0	100.0	99.8	99.9
Oxacillin	50.9	48.5	51.8	60.1	52.6
<i>S. pneumoniae</i> (434)	(399)	(267)	(78)	(1,178)	
Ceftaroline	100.0	100.0	100.0	100.0	100.0
Ceftriaxone	84.8	86.7	87.6	89.7	86.4
<i>E. coli</i> (167)	(91)	(118)	(88)	(464)	
Ceftaroline	91.6	83.5	92.4	84.1	88.8
Ceftriaxone	95.2	89.0	94.9	89.8	92.9
<i>Klebsiella</i> spp. (255)	(52)	(48)	(34)	(389)	
Ceftaroline	92.5	88.5	93.8	76.5	90.7
Ceftriaxone	95.3	90.4	95.8	88.2	94.1

## Introduction

Antimicrobial resistance has been the subject of increasing concern to pediatricians and it remains a major focus of clinical and microbiology research for pediatric infectious diseases specialists. The major challenges to pediatricians are antimicrobial resistance among community-acquired respiratory tract infections and among infections acquired in the healthcare setting. Moreover, the emergence and dissemination of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) represents another important challenge for those physicians treating children. Although much has been reported about antimicrobial susceptibility in the pediatric population, considerably less is understood regarding resistance profile patterns by pediatric patient age groupings.

Ceftaroline, the active metabolite of ceftaroline fosamil, is a cephalosporin with potent bactericidal activity against resistant gram-positive organisms, including MRSA and multidrug-resistant (MDR) *Streptococcus pneumoniae*, and common gram-negative organisms, but not those producing extended-spectrum  $\beta$ -lactamases (ESBLs). Ceftaroline fosamil is approved by the United States (USA) Food and Drug Administration (FDA) for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults, including ABSSSI caused by MRSA. It is approved by the European Medicines Agency (EMA) for similar indications. As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, a global ceftaroline surveillance study, we evaluated the activity of ceftaroline tested against contemporary indicated pathogens causing infections in pediatric patients from USA hospitals.

## Methods

**Organism collection:** A total of 5,291 consecutive unique pediatric patient isolates of clinical significance were collected from 157 USA medical centers as part of the AWARE Program in 2012. These organisms included *S. aureus* (2,117 strains, 47.4% MRSA), *Streptococcus pneumoniae* (1,178; 15.7% penicillin-non-susceptible [MIC,  $\geq 4$   $\mu$ g/mL]), *Haemophilus influenzae* (587),  $\beta$ -hemolytic streptococci (BHS; 556), *Escherichia coli* (464; 7.8% ESBL-phenotype) and *Klebsiella* spp. (389; 7.2% ESBL-phenotype). Susceptibility results were analyzed according to patient age as follows:  $\leq 1$  years old (yo; 1,857 strains); 2-5 yo (1,342); 6-12 yo (1,281) and 13-17 yo (811). Species identification was performed at the participant center and confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA), following manufacturer instructions.

**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 comparator antimicrobials. Validated MIC panels were manufactured by ThermoFisher Scientific (Cleveland, Ohio, USA). *S. aureus* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB), fastidious streptococci were tested in CA-MHB supplemented with 2.5-5% lysed horse blood and *Haemophilus* spp. strains were tested in Haemophilus Test Medium (HTM) according to CLSI document M07-A9 (2012). Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. Susceptibility percentages and validation of QC results were based on CLSI guidelines and susceptibility breakpoints (M100-S23; 2013).

## Results

- Ceftaroline was consistently active against *S. aureus* isolates from all four age groups (MIC<sub>50/90</sub>: 0.25-0.5/1  $\mu$ g/mL; 99.8-100.0% susceptibility). Furthermore, 99.8% of MRSA were susceptible to ceftaroline (MIC<sub>50/90</sub>: 0.5/1  $\mu$ g/mL; Tables 1 and 2). MRSA rates were slightly lower in isolates from patients 13-17 yo (39.9%) compared to other age groups (48.2 – 51.5%). Also, susceptibility to levofloxacin was lower in *S. aureus* isolates from patients 2-5 yo (67.6%) compared to other age groups (74.0 – 76.7%). Susceptibility rates to erythromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole among *S. aureus* did not vary significantly across tabulated age groups (Table 3).
- When tested against methicillin-susceptible *S. aureus* (MSSA), ceftaroline (MIC<sub>50</sub> and MIC<sub>90</sub>: 0.25  $\mu$ g/mL) was 16-fold more active than ceftriaxone (MIC<sub>50</sub> and MIC<sub>90</sub>: 4  $\mu$ g/mL; data not shown)
- All *S. pneumoniae* strains (1,178) were ceftaroline-susceptible (MIC<sub>50/90</sub>:  $\leq 0.015/0.12$   $\mu$ g/mL; Table 1), while ceftriaxone susceptibility varied from only 84.8 ( $\leq 1$  yo) to 89.7% (13-17 yo; Table 3). In general, susceptibility rates for all comparator agents were slightly lower among *S. pneumoniae* isolates from patients  $\leq 1$  yo compared to the other age groups (Table 3). Ceftaroline was highly active against penicillin-non-susceptible *S. pneumoniae* (MIC,  $\geq 4$   $\mu$ g/mL; 185 strains) with MIC<sub>50</sub> and MIC<sub>90</sub> values of 0.25  $\mu$ g/mL (100.0% susceptibility; Table 1), whereas ceftriaxone (MIC<sub>50</sub> and MIC<sub>90</sub>: 2  $\mu$ g/mL; 20.5% susceptibility), amoxicillin/clavulanate (3.2%), erythromycin (0.5%), clindamycin (6.5%) tetracycline (8.1%) and trimethoprim/sulfamethoxazole (2.2%) displayed very limited activity against these organisms (Table 3)

- Ceftaroline was 8-fold more active than ceftriaxone (MIC<sub>90</sub>: 2  $\mu$ g/mL) when tested against penicillin-susceptible (MIC<sub>50/90</sub>:  $\leq 0.015/0.12$  and  $\leq 0.06/1$   $\mu$ g/mL, respectively) and penicillin-non-susceptible *S. pneumoniae* strains (MIC<sub>50/90</sub>: 0.25/0.25 and 2/2  $\mu$ g/mL, respectively; data not shown)
- The highest ceftaroline MIC among *H. influenzae* (587 strains) was only 0.12  $\mu$ g/mL (100.0% susceptibility), and  $\beta$ -lactamase production rates varied from 24.2 (13-17 yo) to 30.1% (6-12 yo); 27.9% overall (Table 3). All isolates were also susceptible to ceftriaxone and levofloxacin, whereas susceptibility to clarithromycin varied from 76.4% (6 – 12 yo) to 90.3% (13-17 yo; Table 3)
- Ceftaroline was also very active against  $\beta$ -hemolytic streptococci (556 strains; highest MIC at 0.06  $\mu$ g/mL). All  $\beta$ -hemolytic streptococcal strains were susceptible to ceftaroline, ceftriaxone and penicillin, but susceptibility to clindamycin varied from 79.1% (2 – 5 yo) to 94.4% (6 – 12 yo; Table 3)
- ESBL-phenotype rates ranged from 5.1 (6 – 12 yo) to 11.4% (13 – 17 yo) among *E. coli*, and from 5.1 ( $\leq 1$  yo) to 14.7% (13 – 17 yo) among *Klebsiella* spp. (Table 3). Ceftaroline exhibited good activity against non-ESBL-phenotype strains of *E. coli* and *Klebsiella* spp. (MIC<sub>90</sub>: 0.25  $\mu$ g/mL for both organisms), but limited activity against ESBL-producing strains (Table 1 and 2).

Table 1. Summary of ceftaroline activity when tested against bacterial isolates from pediatric patients (USA, 2012)

Organism (no. tested)	No. of isolates (cumulative %) inhibited at MIC ( $\mu$ g/mL) of:												MIC <sub>50</sub>	MIC <sub>90</sub>			
	$\leq 0.015$	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32			>32		
<i>S. aureus</i> (2,117)	--	1 (0.0)	5 (0.3)	100 (5.0)	964 (90.5)	635 (80.5)	410 (99.9)	2 (100.0)	--	--	--	--	--	--	--	0.25	1
MSSA (1,113)	--	1 (0.1)	5 (0.5)	100 (9.5)	946 (94.5)	61 (100.0)	410 (99.8)	2 (100.0)	--	--	--	--	--	--	--	0.25	0.25
MRSA (1,004)	--	--	--	--	18 (1.8)	574 (59.0)	410 (99.8)	2 (100.0)	--	--	--	--	--	--	--	0.5	1
<i>S. pneumoniae</i> (1,178)	662 (56.2)	105 (65.1)	103 (73.9)	208 (91.5)	90 (99.2)	10 (100.0)	--	--	--	--	--	--	--	--	--	$\leq 0.015$	0.12
penicillin-S (MIC, $\geq 2$ $\mu$ g/mL; 993)	662 (66.7)	105 (77.2)	102 (87.5)	124 (100.0)	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	0.12
penicillin-I (MIC, 4 $\mu$ g/mL; 165)	--	--	1 (0.6)	84 (51.5)	76 (97.6)	4 (100.0)	--	--	--	--	--	--	--	--	--	0.12	0.25
penicillin-R (MIC, $\geq 8$ $\mu$ g/mL; 20)	--	--	--	--	14 (70.0)	6 (100.0)	--	--	--	--	--	--	--	--	--	0.25	0.5
<i>H. influenzae</i> (587)	486 (82.8)	73 (95.2)	21 (98.8)	7 (100.0)	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	0.03
$\beta$ -lactamase-negative (423)	381 (90.1)	37 (98.8)	5 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	$\leq 0.015$
$\beta$ -lactamase-positive (164)	105 (64.0)	36 (86.0)	16 (95.7)	7 (100.0)	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	0.06
$\beta$ -hemolytic streptococci (556)	523 (94.1)	32 (99.8)	1 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	$\leq 0.015$
Group A Streptococcus (425)	424 (99.8)	1 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	$\leq 0.015$
Group B Streptococcus (112)	87 (77.7)	24 (99.1)	1 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	0.03
Group C Streptococcus (19)	12 (63.2)	7 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	--	$\leq 0.015$	0.03
<i>E. coli</i> (464)	6 (1.3)	60 (14.2)	149 (46.3)	136 (75.6)	39 (84.1)	22 (88.8)	9 (90.7)	5 (91.8)	4 (92.7)	5 (93.8)	1 (94.0)	1 (94.2)	27 (100.0)	0.12	1	0.12	1
non-ESBL-phenotype (428)	6 (1.4)	60 (15.4)	149 (50.2)	136 (82.0)	38 (90.9)	22 (96.0)	9 (98.1)	4 (99.1)	2 (99.5)	2 (100.0)	--	--	--	--	--	0.06	0.25
ESBL-phenotype (36)	--	--	--	--	1 (2.8)	0 (2.8)	0 (2.8)	1 (5.6)	2 (11.1)	3 (19.4)	1 (22.2)	1 (25.0)	27 (100.0)	>32	>32	--	--
<i>Klebsiella</i> spp. (389)	1 (0.3)	6 (1.8)	123 (33.4)	129 (66.6)	66 (83.5)	28 (90.7)	7 (92.5)	3 (93.3)	4 (94.3)	3 (95.1)	1 (95.4)	0 (95.4)	18 (100.0)	0.12	0.5	0.12	0.5
non-ESBL-phenotype (361)	1 (0.3)	6 (1.9)	123 (36.0)	129 (71.7)	66 (90.0)	27 (97.5)	6 (99.2)	2 (99.7)	1 (100.0)	--	--	--	--	0.12	0.25	--	--
ESBL-phenotype (28)	--	--	--	--	1 (3.6)	1 (7.1)	1 (10.7)	4 (25.0)	2 (32.1)	1 (35.7)	0 (35.7)	18 (100.0)	>32	>32	>32	--	--

Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; S = susceptible; I = intermediate; R = resistant; and ESBL = extended spectrum  $\beta$ -lactamase.

Table 2. Summary of ceftaroline activity tested against bacterial isolates from pediatric patients stratified by age group (USA, 2012)

Organisms/subgroup (no. tested)	Ceftaroline activity by age group:															
	$\leq 1$ year old				2-5 years old				6-12 years old				13-17 years old			
	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	%S	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	%S	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	%S	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	%S
<i>S. aureus</i>	633	0.5	1	99.8	493	0.5	1	100.0	527	0.25	1	100.0	464	0.25	1	99.8
MSSA	322	0.25	0.25	100.0	239	0.25	0.25	100.0	273	0.25	0.25	100.0	279	0.25	0.25	100.0
MRSA	311	0.5	1	99.7	254	0.5	1	100.0	254	0.5	1	100.0	185	0.5	1	99.5
<i>S. pneumoniae</i>	434	$\leq 0.015$	0.12	100.0	399	$\leq 0.015$	0.12	100.0	267	$\leq 0.015$	0.12	100.0	78	$\leq 0.015$	0.12	100.0
<i>H. influenzae</i>	241	$\leq 0.015$	0.03	100.0	161	$\leq 0.015$	0.03	100.0	123	$\leq 0.015$	0.03	100.0	62	$\leq 0.015$	0.03	100.0
<i>E. coli</i>	167	0.12	0.5	91.6	91	0.12	4	83.5	118	0.06	0.5	92.4	88	0.12	4	84.1
Non-ESBL-phenotype	157	0.12	0.5	96.8	81	0.12	0.25	93.8	112	0.06	0.25	97.3	78	0.12	0.5	94.9
ESBL-phenotype	10	>32	>32	10.0	10	>32	>32	0.0	6	>32	NA	0.0	10	32	>32	0.0
<i>Klebsiella</i> spp.	255	0.12	0.5	92.5	52	0.12	4	88.5	48	0.06	0.5	93.8	34	0.12	>32	76.5
Non-ESBL-phenotype	242	0.12	0.5	97.5	46	0.12	0.5	100.0	44	0.06	0.25	100.0	29	0.12	1	89.7
ESBL-phenotype	13	>32	>32	0.0	6	>32	NA	0.0	4	4	NA	25.0	5	>32	NA	0.0

Abbreviations: %S = percentage susceptible by the CLSI criteria [CLSI, 2013]; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; ESBL = extended spectrum  $\beta$ -lactamase and NA = not applicable due to reduced number of strains (<10).

Table 3. Activity of ceftaroline and comparator antimicrobial agents when tested against bacterial isolates from pediatric patients in USA medical centers (2012)

Organism / Antimicrobial agent	% Susceptible by CLSI criteria* (no. tested)				
	$\leq 1$ year old	2-5 years old	6-12 years old	13-17 years old	All ( $\leq 17$ years old)
<i>Staphylococcus aureus</i>	(633)	(493)	(527)	(464)	(2,117)
Ceftaroline	99.8	100.0	100.0	99.8	99.9
Oxacillin	50.9	48.5	51.8	60.1	52.6
Erythromycin	38.9	35.0	40.8	42.1	39.6
Clindamycin	93.8	94.3	93.3	91.8	92.8
Levofloxacin	76.7	67.6	74.0	76.5	73.9
Tetracycline	98.3	98.4	96.2	96.3	97.3
TMP/SMX*	99.8	98.4	99.6	99.6	99.4
MSSA	(322)	(			