C2-124

Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Contemporary (2010) Pathogens Associated with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Isolated from the Asia-Pacific Region (APAC) and South Africa (SAF)

PR RHOMBERG, RK FLAMM, RN JONES, HS SADER

JMI Laboratories, North Liberty, Iowa, USA

ICAAC 2012
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
paul-rhomberg@jmilabs.com

Abstract

Background: Ceftaroline (CPT), the active form of CPT fosamil, is a novel cephalosporin with broad-spectrum *in vitro* bactericidal activity against methicillin-susceptible (MS) and -resistant (MR) *S. aureus* (SA), ß-hemolytic streptococci (BHS) and Enterobacteriaceae (ENT). CPT fosamil is approved by the USA-FDA for treatment of ABSSSI and community-acquired bacterial pneumonia (CABP).

Methods: CLSI broth microdilution susceptibility testing methods were utilized for determining MIC results for CPT and comparators on pathogens associated with ABSSSI collected in 2010 from 25 medical centers located in Australia (AUS), China, Hong Kong, Malaysia, Singapore, South Korea, Thailand and SAF.

Results: CPT was very active against SA with a four- to eight-fold MIC increase among MRSA ($MIC_{50/90}$, 1/2 µg/ml) compared to MSSA ($MIC_{50/90}$, 0.25 µg/ml). CPT was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/>8 µg/ml) against SA. CPT MIC values against SA were similar between countries, except for a lower MIC_{90} (0.5 µg/ml; n=466) in AUS, whereas MRSA rates varied greatly from 71.2% (47/66, Singapore) to 22.2% (6/27, Malaysia). All SA were S to vancomycin, linezolid and daptomycin. *S. pyogenes* (MIC_{90}, ≤0.008 µg/ml) were more susceptible to CPT than *S. agalactiae* and other BHS. Non ESBL-producing *E. coli* (MIC_{90}, 0.5 µg/ml; n=289) and *K. pneumoniae* (MIC_{90}, 0.25 µg/ml; n=233) were generally S to CPT, however ESBL-producing strains (*E. coli*, n=244; *K. pneumoniae*, n=144) had elevated CPT results ($MIC_{50/90}$, >32 µg/ml).

Organism	Ceftaroline MIC value in µg/ml: MIC_{50}	MIC_{90}
S. aureus (1080)	0.25	1
MSSA (673)	0.25	0.25
MRSA (407)	1	2
ß-hemolytic strep (297)	≤0.008	0.015
S. pyogenes (97)	≤0.008	≤0.008
S. agalactiae (141)	0.015	0.03
Other BST (59)	≤0.008	0.015

Conclusions: CPT demonstrated potent *in vitro* activity against recent pathogens associated with ABSSSI. This occurred in spite of differing MRSA and other antimicrobial resistance rates among the nations across APAC and SAF.

Introduction

Ceftaroline fosamil is an N-phosphonoamino water-soluble prodrug cephalosporin. Its bioactive form, ceftaroline, is rapidly released *in vivo*. Ceftaroline fosamil was approved in 2010 by the United States (USA) Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). In ABSSSI, ceftaroline fosamil is indicated for infections caused by *Staphylococcus aureus* (including methicillin susceptible and -resistant isolates)*, Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae,* and *Klebsiella oxytoca*.

In this study we evaluated the activity of ceftaroline compared to other broad-spectrum comparison agents when tested against contemporary clinical isolates collected in Asia-Pacific (APAC) and South Africa (SAF) medical centers from January through December 2010, as part of the AWARE surveillance program.

Materials and Methods

Consecutively collected, unique isolates from patients with clinically significant infections (bloodstream, respiratory, skin and skin structure) were collected in 2010 from 25 medical centers in Australia, China, Hong Kong, Malaysia, Singapore, South Korea, Thailand and South Africa.

Reference broth microdilution test methods (Clinical and Laboratory Standards Institute; CLSI) were conducted to determine antimicrobial susceptibility of ceftaroline and comparator agents. Validated MIC panels were manufactured by ThermoFisher Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). *S. aureus* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). ß-hemolytic streptococci were tested in CA-MHB supplemented with 2.5-5% lysed horse blood (M07-A9, 2012).

Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. QC strains included: *S. aureus* ATCC 29213, *E. coli* ATCC 25922 and ATCC 35218, and *Streptococcus pneumoniae* ATCC 49619. Susceptibility percentages and validation of QC results were based on CLSI guidelines (M100-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). The interpretive criteria used for ceftaroline were those published in the USA-FDA package insert (2012). The ESBL-phenotype for *Klebsiella* spp. and *E. coli* was defined as a MIC ≥2 µg/ml for ceftazidime or ceftriaxone (M100-S22).

Results

- Table 1 shows the geographic distribution of isolates collected in the 2010 APAC and SAF surveillance. The number of isolates per country ranged from 82 from Malaysia to 929 from China.
- Table 2 shows the MIC frequency distribution for ceftaroline against the APAC and SAF isolates and Tables 3 and 4 show the activity of ceftaroline and comparators tested against Gram-positive and -negative pathogens, respectively.
- The percent of *S. aureus* which were methicillin-resistant (MRSA) varied greatly from 71.2% (47/66, Singapore) to 22.2% (6/27, Malaysia) with an overall rate in the APAC and SAF of 37.7%. Ceftaroline exhibited activity against methicillin-susceptible *S. aureus* (MSSA) isolates (MIC_{50} and MIC_{90}, 0.25 µg/ml) and MRSA isolates ($MIC_{50/90}$, 1/2 µg/ml). The highest ceftaroline MIC results observed among MSSA and MRSA were 1 and 8 µg/ml, respectively (Table 3). 90.4% of all *S. aureus* and 74.4% of MRSA were inhibited at a ceftaroline MIC of ≤1 µg/ml and all but three *S. aureus* isolates were inhibited at a ceftaroline MIC of ≤2 µg/ml (Table 2). These three MRSA isolates were from the same medical center in Thailand and had ceftaroline MIC values >2 µg/ml (two with MIC of 4 µg/ml, one with MIC of 8 µg/ml; Table 2).
- Ceftaroline was 16-fold more active than ceftriaxone when tested against MSSA. Susceptibility for agents against MSSA was >90% except for erythromycin (75.6% susceptible), tetracycline (86.8-87.2%; EUCAST and CLSI interpretive criteria, respectively) and clindamycin (89.3-89.9%; Table 3).
- The most active agents against MRSA were: ceftaroline ($MIC_{50/90}$, 1/2 µg/ml; 74.4% susceptible and 99.3% inhibited at ≤2 µg/ml), linezolid ($MIC_{50/90}$, 1/2 µg/ml; 100% susceptible), vancomycin ($MIC_{50/90}$, 1/1 µg/ml; 100.0% susceptible), and daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml; 100.0% susceptible; Table 3). In contrast, only 26.3% of MRSA strains were susceptible to levofloxacin (Table 3).
- Against ß-hemolytic streptococci, ceftaroline demonstrated greater activity ($MIC_{50/90}$, ≤0.008/0.015 µg/ml) than penicillin ($MIC_{50/90}$, ≤0.03/0.06 µg/ml) and ceftriaxone ($MIC_{50/90}$, ≤0.06/0.12 µg/ml). Decreased susceptibility was observed only with erythromycin (67.0%) and clindamycin (76.4-77.4% susceptible, CLSI and EUCAST interpretive criteria, respectively; Table 3).
- Amongst ß-hemolytic streptococci, ceftaroline was slightly more active against Group A strains ($MIC_{50/90}$, ≤0.008/≤0.008 µg/ml) when compared to Group B ($MIC_{50/90}$, 0.015/0.03 µg/ml) and other ß-hemolytic streptococci ($MIC_{50/90}$, ≤0.008/0.015 µg/ml; Tables 2 and 3).
- *E. coli* isolates were generally susceptible to ceftaroline (MIC_{50}, 0.5 µg/ml; Tables 2 and 4). Among non-ESBL strains, 93.8 and 97.0% of strains were inhibited at ceftaroline MIC of ≤0.5 and ≤1 µg /ml, respectively (MIC_{50}, 0.12 µg/ml and MIC_{90}, 0.5 µg/ml; Tables 2 and 4), while ESBL-phenotype strains were less susceptible to ceftaroline (MIC_{50} and MIC_{90}, >32 µg/ml) and other cephalosporins tested (Table 4).
- Ceftaroline was active against non-ESBL *K. pneumoniae* strains with a $MIC_{50/90}$ of 0.12/0.25 µg/ml, (Table 4) and 96.6% of strains were inhibited at ≤0.5 µg/ml. In contrast, the ESBL-phenotype strains showed elevated ceftaroline MIC values (MIC_{50} and MIC_{90}, >32 µg/ml). Resistance rates to "third- and fourth-generation" cephalosporins were high among ESBL-phenotype *K. pneumoniae* (93.8 and 62.5% resistant to ceftriaxone and ceftazidime, respectively, according to CLSI breakpoints; Table 4).
- *K. pneumoniae* and *K. oxytoca* exhibited similar susceptibility to ceftaroline. Among non-ESBL strains, $MIC_{50/90}$, results were 0.12/0.25 and 0.06/0.12 µg/ml for *K. pneumoniae* and *K. oxytoca*, respectively (Table 4). Decreased susceptibility to meropenem (MIC, ≥2 µg/ml) was observed in 13.9% of ESBL-phenotype *K. pneumoniae* [Table 4] and 10.0% [1/10] isolates) of ESBL-phenotype *K. oxytoca* (Table 4). These results suggest the production of a carbapenemase such as KPC. The great majority (21/23 isolates) of meropenem non-susceptible *Klebsiella* spp. (twenty *K. pneumoniae* and one *K. oxytoca*) were found in five medical centers in China with the remaining two strains found in South Korea and South Africa.
- Ceftaroline showed variable activity against the 88 isolates of *Morganella morganii* (MIC_{50}, 0.12 µg/ml and MIC_{90}, >32 µg/ml; Table 4). Overall, 70.0% of strains were inhibited at ≤1 µg/ml of ceftaroline (Table 2) and 90.9 and 92.0% of strains according to CLSI interpretive criteria were susceptible to ceftriaxone and ceftazidime, respectively (Table 4).

Table 1. *Geographic Distribution of Isolates Processed in the 2010 APAC and SAF Surveillance.*

Organism or group	No.(%) of organisms by country: Australia	China	Hong Kong	Korea	Malaysia	Singapore	South Africa	Thailand	Overall
Staphylococcus aureus	466 (43.2)	327 (30.3)	38 (3.5)	74 (6.9)	27 (2.5)	66 (6.1)	46 (4.3)	36 (3.3)	1080
ß-hemolytic streptococci	118 (39.7)	72 (29.2)	12 (4.0)	38 (12.8)	17 (5.7)	11 (3.7)	16 (5.4)	13 (4.4)	297
Escherichia coli	128 (24.0)	293 (55.0)	30 (5.6)	20 (3.8)	7 (1.3)	13 (2.4)	13 (2.4)	29 (5.4)	533
Klebsiella pneumoniae	52 (13.8)	194 (51.5)	14 (3.7)	28 (7.4)	29 (7.7)	13 (3.5)	29 (7.7)	18 (4.8)	377
Klebsiella oxytoca	10 (43.5)	10 (43.5)	0 (0)	2 (8.7)	1 (4.4)	0 (0)	0 (0)	0 (0)	23
Morganella morganii	28 (31.8)	33 (37.5)	6 (6.8)	15 (17.0)	1 (1.1)	4 (4.5)	0 (0)	1 (1.1)	88
Total	802 (33.4)	929 (38.7)	100 (4.2)	177 (7.4)	82 (3.4)	107 (4.5)	104 (4.3)	97 (4.0)	2398

Table 2. *MIC Frequency Distributions of Ceftaroline Tested Against Pathogen Groups in the 2010 APAC and SAF Surveillance.*

Organism (no. of isolates)	No. of isolates (%) inhibited at antimicrobial MIC (µg/ml): ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Staphylococcus aureus (1080)	-	-	1 (0.1)	1 (0.1)	80 (7.4)	567 (52.5)	166 (15.4)	161 (14.9)	101 (9.4)	2 (0.2)	1 (0.1)	-	-	-	0.25	1
MSSA (673)	-	-	1 (0.1)	1 (0.1)	80 (11.9)	563 (83.7)	27 (4.0)	1 (0.1)	-	-	-	-	-	-	0.25	0.25
MRSA (407)	-	-	-	-	-	4 (1.0)	139 (34.2)	160 (39.3)	101 (24.8)	2 (0.5)	1 (0.2)	-	-	-	1	2
ß-hemolytic streptococci (297)	152 (51.2)	125 (42.1)	19 (6.4)	1 (0.3)	-	-	-	-	-	-	-	-	-	-	≤0.008	0.015
Group A *Streptococcus* (97)	97 (100.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	≤0.008	≤0.008
Group B *Streptococcus* (141)	6 (4.3)	119 (84.4)	16 (11.3)	-	-	-	-	-	-	-	-	-	-	-	0.015	0.03
Other ß-hemolytic streptococci (59)	49 (83.1)	6 (10.2)	3 (5.1)	1 (1.7)	-	-	-	-	-	-	-	-	-	-	≤0.008	0.015
Escherichia coli (533)	-	2 (0.4)	25 (4.7)	98 (18.4)	109 (20.5)	25 (4.7)	13 (2.4)	10 (1.9)	7 (1.3)	2 (0.4)	5 (0.9)	1 (0.2)	3 (0.6)	233 (43.7)	0.5	>32
non ESBL (289)	-	2 (0.7)	25 (8.7)	98 (33.9)	109 (37.7)	25 (8.7)	12 (4.2)	9 (3.1)	7 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0.12	0.5
ESBL phenotype (244)	-	-	-	-	-	-	1 (0.4)	1 (0.4)	0 (0.0)	2 (0.8)	5 (2.0)	1 (0.4)	2 (0.8)	232 (95.1)	>32	>32
Klebsiella pneumoniae (377)	1 (0.3)	2 (0.5)	13 (3.4)	92 (24.4)	82 (21.8)	25 (6.6)	11 (2.9)	5 (1.3)	7 (1.9)	6 (1.6)	3 (0.8)	5 (1.3)	2 (0.5)	123 (32.6)	0.12	>32
non ESBL (233)	1 (0.4)	2 (0.9)	13 (5.6)	92 (39.5)	82 (35.2)	25 (10.7)	10 (4.3)	5 (2.1)	2 (0.9)	1 (0.4)	-	-	-	-	0.12	0.25
ESBL phenotype (144)	-	-	-	-	-	-	1 (0.7)	0 (0.0)	5 (3.5)	5 (3.5)	3 (2.1)	5 (3.5)	2 (1.4)	123 (85.4)	>32	>32
Klebsiella oxytoca (23)	-	-	-	7 (30.4)	5 (21.7)	0 (0.0)	1 (4.3)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	8 (34.8)	0.12	>32
non ESBL (13)	-	-	-	7 (53.8)	5 (38.5)	0 (0.0)	1 (7.7)	-	-	-	-	-	-	-	0.06	0.12
ESBL phenotype (10)	-	-	-	-	-	-	-	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	8 (80.0)	>32	>32
Morganella morganii (88)	-	-	4 (4.5)	18 (20.5)	24 (27.3)	12 (13.6)	5 (5.7)	3 (3.4)	2 (2.3)	0 (0.0)	5 (5.7)	1 (1.1)	3 (3.4)	11 (12.5)	0.12	>32

Table 3. *Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against S. aureus and ß-hemolytic streptococci Collected from the 2010 APAC and SAF Surveillance.*

Antimicrobial agent (tested)	MIC (µg/ml): MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (1080)					
Ceftaroline	0.25	1	0.03 – 8	90.4[b] / -	- / -
Ceftriaxone	4	>8	0.25 – >8	60.7[c] / 37.7	62.3 / 37.7
Erythromycin	0.5	>4	≤0.25 – >4	57.3 / 41.7	57.3 / 42.1
Clindamycin	≤0.25	>2	≤0.25 – >2	74.6 / 25.4	74.3 / 25.4
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.5	>8	≤0.25 – >8	70.2 / 29.5	69.8 / 30.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	68.3 / 31.2	68.3 / 31.2
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5 – >4	90.2 / 9.8	90.2 / 9.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
MSSA (673)					
Ceftaroline	0.25	0.25	0.03 – 1	100.0[b] / -	- / -
Ceftriaxone[c]	4	4	0.25 – 8	97.5[c] / 0.0	100.0 / 0.0
Erythromycin	0.5	>4	≤0.25 – >4	75.6 / 24.1	75.6 / 24.1
Clindamycin	≤0.25	>2	≤0.25 – >2	89.9 / 10.1	89.3 / 10.1
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.5	>8	≤0.25 – >8	87.2 / 12.5	86.8 / 12.9
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	93.8 / 5.9	93.8 / 5.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	98.1 / 1.9	98.1 / 1.5
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
MRSA (407)					
Ceftaroline	1	2	0.25 – 8	74.4[b] / -	- / -
Ceftriaxone[c]	>8	>8	8 – >8	0.0[c] / 100.0	0.0 / 100.0
Erythromycin	>4	>4	≤0.25 – >4	27.0 / 70.8	27.0 / 72.0
Clindamycin	>2	>2	≤0.25 – >2	49.4 / 50.6	49.4 / 50.6
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	42.0 / 57.7	41.8 / 58.2
Levofloxacin	>4	>4	≤0.5 – >4	26.3 / 73.0	26.3 / 73.0
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	77.1 / 22.9	77.1 / 21.4
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
ß-hemolytic streptococci (297)[d]					
Ceftaroline	≤0.008	0.015	≤0.008 – 0.06	- / -	- / -
Penicillin	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	67.0 / 31.6	67.0 / 31.6
Clindamycin	≤0.25	>2	≤0.25 – >2	76.4 / 22.6	77.4 / 22.6
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	39.4 / 58.9	39.1 / 60.6
Levofloxacin	≤0.5	1	≤0.5 – >4	92.9 / 7.1	90.6 / 7.1
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Streptococcus pyogenes (97)					
Ceftaroline	≤0.008	≤0.008	≤0.008	100.0[b] / -	- / -
Penicillin	≤0.03	≤0.03	≤0.03	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	86.6 / 13.4	86.6 / 13.4
Clindamycin	≤0.25	>2	≤0.25 – >2	88.7 / 11.3	88.7 / 11.3
Vancomycin	0.5	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	66.0 / 33.0	66.0 / 34.0
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0 / 0.0	96.9 / 0.0
Daptomycin	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Streptococcus agalactiae (141)					
Ceftaroline	0.015	0.03	≤0.008 – 0.03	100.0[b] / -	- / -
Penicillin	0.06	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	52.5 / 45.4	52.5 / 45.4
Clindamycin	≤0.25	>2	≤0.25 – >2	63.8 / 34.0	66.0 / 34.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	17.0 / 83.0	17.0 / 83.0
Levofloxacin	1	>4	≤0.5 – >4	85.8 / 14.2	84.4 / 14.2
Daptomycin	0.25	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied [Teflaro Product Insert, 2012].
c. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Rocephin Product Insert, 2012].
d. Includes: *Streptococcus dysgalactiae* (1 strain), *Streptococcus pyogenes* (97 strains), *Streptococcus agalactiae* (141 strains), Group C *Streptococcus* (17 strains), Group F *Streptococcus* (1 strain), and Group G *Streptococcus* (40 strains).

Table 4. *Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against E. coli, Klebsiella spp, and Morganella morganii Collected from the 2010 APAC and SAF Surveillance.*

Antimicrobial agent (tested)	MIC (µg/ml): MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
E. coli (533)					
Ceftaroline	0.5	>32	0.015 – >32	51.0[b] / 47.1	- / -
Ceftazidime	0.25	16	0.03 – >32	79.0 / 14.8	68.9 / 21.0
Piperacillin/tazobactam	2	4	≤0.5 – >64	96.2 / 2.3	93.2 / 3.8
Ceftriaxone	0.12	>8	≤0.06 – >8	54.6 / 45.4	54.6 / 45.4
Gentamicin	≤1	>8	≤1 – >8	61.5 / 38.1	60.6 / 38.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	53.3 / 43.9	52.3 / 46.7
Meropenem	≤0.12	≤0.12	≤0.12 – 8	99.8 / 0.2	99.8 / 0.0
Non-ESBL *E. coli* (289)					
Ceftaroline	0.12	0.5	0.015 – >32	93.8[b] / 3.1	- / -
Ceftazidime	0.12	0.25	0.03 – 1	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	≤0.5 – >64	97.2 / 1.7	96.5 / 2.8
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤1	>8	≤1 – >8	79.6 / 20.1	78.9 / 20.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	77.5 / 20.4	76.5 / 22.5
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
ESBL phenotype *E. coli* (244)					
Ceftaroline	>32	>32	0.5 – >32	0.4[b] / 99.2	- / -
Ceftazidime	4	32	0.25 – >32	54.1 / 32.4	32.0 / 45.9
Piperacillin/tazobactam	4	16	1 – >64	95.1 / 2.9	89.3 / 4.9
Ceftriaxone	>8	>8	0.25 – >8	0.8 / 99.2	0.8 / 99.2
Gentamicin	>8	>8	≤1 – >8	40.2 / 59.4	38.9 / 59.8
Levofloxacin	>4	>4	≤0.5 – >4	24.6 / 71.7	23.8 / 75.4
Meropenem	≤0.12	≤0.12	≤0.12 – 8	99.6 / 0.4	99.6 / 0.0
K. pneumonaie (377)					
Ceftaroline	0.12	>32	≤0.008 – >32	59.9[b] / 38.7	- / -
Ceftazidime	0.25	>32	≤0.015 – >32	71.6 / 23.9	66.8 / 28.4
Piperacillin/tazobactam	4	>64	≤0.5 – >64	80.9 / 11.7	73.2 / 19.1
Ceftriaxone	≤0.06	>8	≤0.06 – >8	63.7 / 35.8	63.7 / 35.8
Gentamicin	≤1	>8	≤1 – >8	75.3 / 24.1	74.5 / 24.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	75.9 / 21.0	73.7 / 24.1
Meropenem	≤0.12	≤0.12	≤0.12 – >8	94.2 / 5.3	94.7 / 4.0
Non-ESBL phenotype *K. pneumoniae* (233)					
Ceftaroline	0.12	0.25	≤0.008 – 4	96.6[b] / 1.3	- / -
Ceftazidime	0.12	0.25	≤0.015 – 1	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	8	≤0.5 – >64	97.4 / 0.9	94.4 / 2.6
Ceftriaxone	≤0.06	0.12	≤0.06 – 1	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤1	≤1	≤1 – >8	97.0 / 2.6	96.1 / 3.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	96.1 / 3.0	95.3 / 3.9
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
ESBL phenotype *K. pneumoniae* (144)					
Ceftaroline	>32	>32	0.5 – >32	0.7[b] / 99.3	- / -
Ceftazidime	32	>32	0.12 – >32	25.7 / 62.5	13.2 / 74.3
Piperacillin/tazobactam	16	>64	1 – >64	54.2 / 29.2	38.9 / 45.8
Ceftriaxone	>8	>8	0.25 – >8	4.9 / 93.8	4.9 / 93.8
Gentamicin	>8	>8	≤1 – >8	40.3 / 59.0	39.6 / 59.7
Levofloxacin	4	>4	≤0.5 – >4	43.1 / 50.0	38.9 / 56.9
Meropenem	≤0.12	>8	≤0.12 – >8	84.7 / 13.9	86.1 / 10.4
K. oxytoca (23)					
Ceftaroline	0.12	>32	0.06 – >32	56.5[b] / 39.1	- / -
Ceftazidime	0.12	32	0.06 – >32	78.3 / 17.4	65.2 / 21.7
Piperacillin/tazobactam	2	>64	≤0.5 – >64	78.3 / 13.0	78.3 / 21.7
Ceftriaxone	≤0.06	>8	≤0.06 – >8	60.9 / 39.1	60.9 / 39.1
Gentamicin	≤1	>8	≤1 – >8	73.9 / 26.1	73.9 / 26.1
Levofloxacin	≤0.5	1	≤0.5 – >4	91.3 / 4.3	91.3 / 8.7
Meropenem	≤0.12	≤0.12	≤0.12 – >8	95.7 / 4.3	95.7 / 4.3
Non-ESBL *K. oxytoca* (13)					
Ceftaroline	0.06	0.12	0.06 – 0.5	100.0[b] / 0.0	- / -
Ceftazidime	0.06	0.12	0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	≤0.5 – 4	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤1	≤1	≤1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
ESBL-phenotype *K. oxytoca* (10)					
Ceftaroline	>32	>32	1 – >32	0.0[b] / 90.0	- / -
Ceftazidime	4	32	0.25 – >32	50.0 / 40.0	20.0 / 50.0
Piperacillin/tazobactam	8	>64	1 – >64	50.0 / 30.0	50.0 / 50.0
Ceftriaxone	>8	>8	0.25 – >8	10.0 / 90.0	10.0 / 90.0
Gentamicin	>8	>8	≤1 – >8	40.0 / 60.0	40.0 / 60.0
Levofloxacin	≤0.5	4	≤0.5 – >4	80.0 / 10.0	80.0 / 20.0
Meropenem	≤0.12	≤0.12	≤0.12 – >8	90.0 / 10.0	90.0 / 10.0
M. morganii (88)					
Ceftaroline	0.12	>32	0.03 – >32	71.6[b] / 25.0	- / -
Ceftazidime	0.12	2	0.03 – >32	92.0 / 6.8	85.2 / 8.0
Piperacillin/tazobactam	≤0.5	1	≤0.5 – 32	98.9 / 0.0	97.7 / 1.1
Ceftriaxone	≤0.06	1	≤0.06 – >8	90.9 / 6.8	90.9 / 6.8
Gentamicin	≤1	>8	≤1 – >8	81.8 / 15.9	80.7 / 18.2
Levofloxacin	≤0.5	2	≤0.5 – >4	92.0 / 4.5	81.8 / 8.0
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied [Teflaro Package Insert, 2012].

Conclusions

- Ceftaroline demonstrated potent *in vitro* broad-spectrum activity against *S. aureus* (including MRSA) and ß-hemolytic streptococci isolated from patients in medical centers during 2010 from Australia, China, Hong Kong, Malaysia, Singapore, South Korea, Thailand and South Africa.
- The activity of ceftaroline against *S. aureus* was similar to that of vancomycin, daptomycin and linezolid; activity against ß-hemolytic streptococci was similar to that of penicillin and ceftriaxone.

Acknowledgements

This study at JMI Laboratories was supported by an Educational/Research Grant from AstraZeneca, and JMI received compensation fees for services in relation to preparing the abstract/poster, which was funded by AstraZeneca.

References

1. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement*. Wayne, PA: CLSI.
3. Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, Critchley I, Das AF, Thye D (2010). Integrated analysis of CANVAS 1 and 2: Phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clin Infect Dis* 51: 641-650.
4. Corey GR, Wilcox MH, Talbot GH (2010). CANVAS 1: The first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 65 Suppl 4: iv41-51.
5. Flamm RK, Sader HS, Farrell DJ, Jones RN (2012). Summary of ceftaroline activity against pathogens in the United States, 2010: Report from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program. *Antimicrob Agents Chemother* 56: 2933-2940.
6. Jones RN, Mendes RE, Sader HS (2010). Ceftaroline activity against pathogens associated with complicated skin and skin structure infections: Results from an international surveillance study. *J Antimicrob Chemother* 65 Suppl 4: iv17-iv31.
7. Rocephin Package Insert (2010). Available at http://www.gene.com/gene/products/information/rocephin/pdf/pi.pdf. Accessed January 2012.
8. Sader HS, Fritsche TR, Jones RN (2008). Antimicrobial activities of ceftaroline and ME1036 tested against clinical strains of community-acquired methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 52: 1153-1155.
9. Teflaro Package Insert (2012). Available at http://www.frx.com/pi/Teflaro_pi.pdf. Accessed June 2012.