Spectrum and Potency of Ceftaroline Against Leading Pathogens Causing Skin and Skin Structure Infections in Europe and South Africa, 2010

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

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
robert-flamm@jmilabs.com

Abstract

Objective: To determine the spectrum and potency of ceftaroline (CPT) against recent (2010) leading pathogens causing complicated skin and skin structure infections (cSSSI) isolated in Europe and South Africa (SAF). CPT, the active metabolite of the prodrug ceftaroline fosamil, is a novel cephalosporin exhibiting broad-spectrum *in vitro* bactericidal activity against Gram-positive organisms, including *Streptococcus pneumoniae* and methicillin-susceptible (MS) and -resistant (MR) *Staphylococcus aureus* (SA), as well as common Gram-negative organisms.

Methods: A total of 2,943 isolates from the 2010 Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Programme were identified as cSSSI pathogens by the infection type and/or specimen type recorded by the submitter. Isolates were collected from patients in 54 medical centres in 19 European countries (including Israel and Turkey) and in SAF (54 isolates, 1 medical centre) during 2010. Susceptibility testing for CPT and commonly used antimicrobials was performed by CLSI broth microdilution methodology. Susceptibility interpretations for the comparators were as published in CLSI and EUCAST guidelines. Extended spectrum beta-lactamase (ESBL) phenotype was determined as per CLSI guidelines.

Results: The potencies of CPT against the leading pathogens isolated are shown in Table 1. CPT was very active overall against SA ($MIC_{50/90}$, 0.25/1 mg/L) and inhibited 100.0% of all isolates at a MIC ≤2 mg/L (see Table 1). Activity against MRSA was good ($MIC_{50/90}$, 1/2 mg/L) but lower than observed against MSSA ($MIC_{50/90}$, 0.25/0.25 mg/L). CPT was also very active against 466 beta-haemolytic streptococci (BHS), including 198 *S. pyogenes* and 142 *S. agalactiae*, and 94 viridans group streptococci (VGS). CPT was very active against *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KPN) not expressing ESBLs but, similar to other extended spectrum beta-lactam agents (ceftriaxone, cefepime and ceftazidime), was not active against the majority of EC and KPN demonstrating an ESBL phenotype.

Conclusions: This study demonstrated the potent *in vitro* activity of CPT against the great majority of recent (2010) pathogens, including MRSA strains, isolated from patients with documented cSSSI from Europe and SAF. These data suggest that ceftaroline fosamil could emerge as an important therapeutic alternative for cSSSI occurring in Europe and SAF.

Introduction

Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil, an N-phosphonoamino water-soluble cephalosporin, with demonstrated *in vitro* activity against typical complicated skin and skin structure infection (cSSSI) pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), streptococci, and enteric Gram-negative bacilli such as non-extended spectrum β-lactamase (non-ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*. In two Phase 3 trials (NCT00424190; NCT00423657), ceftaroline fosamil was shown to be non-inferior to vancomycin plus aztreonam for the treatment of patients with cSSSI. Ceftaroline fosamil was approved in 2010 by the United States Food and Drug Administration (USA-FDA) for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.

In this study, we evaluated ceftaroline and comparator antimicrobial agents against 2,495 isolates (of 2,943 total) of the leading cSSSI pathogens collected in European and South African hospitals during 2010 as part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Programme, a global ceftaroline surveillance study.

Materials and Methods

Organism Collection: A total of 2,943 isolates from the 2010 AWARE Programme were identified as cSSSI pathogens by the infection type and/or specimen type recorded by the submitter. Isolates were collected from patients in 54 medical centres in 19 European countries (including Israel and Turkey) and in South Africa (54 isolates, 1 medical centre) during 2010. European countries (number of centres) were: Belgium (1), Czech Republic (1), France (5), Germany (7), Greece (2), Hungary (1), Israel (1), Italy (6), Netherlands (1), Poland (1), Portugal (1), Romania (1), Russia (5), Slovenia (1), Spain (7), Sweden (2), Turkey (5), United Kingdom (4), Ukraine (1). Of the total, 2,495 isolates of the leading pathogens are described in this study.

Susceptibility Testing: Isolates were susceptibility tested against ceftaroline and comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012). Isolates were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). CA-MHB supplemented with 3–5% lysed horse blood was used for streptococci (M07-A9, 2012). Susceptibility percentages and validation of quality control (QC) results were based on the CLSI guidelines (M100-S22), and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). In the absence of CLSI/EUCAST interpretive criteria, USA-FDA breakpoints were applied for ceftaroline and ceftriaxone. ESBL phenotype was determined as per CLSI guidelines (M100-S22). Concurrent QC testing was performed to assure proper test conditions and procedures. QC strains included: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619. All QC results were within published ranges.

Results

- Ceftaroline exhibited activity against methicillin-susceptible *S. aureus* (MSSA) isolates (MIC_{50} and MIC_{90}, 0.25 mg/L) and MRSA isolates ($MIC_{50/90}$, 1/2 mg/L). The highest MIC results observed among MSSA and MRSA were 0.5 and 2 mg/L, respectively (Tables 1 and 2).
- Ceftaroline was 16-fold more active than ceftriaxone when tested against MSSA. All tested agents were ≥93.7% susceptible when tested against MSSA, except erythromycin (86.3% susceptible; Table 2).
- The most active agents against MRSA were: linezolid ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible), vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible), and ceftaroline ($MIC_{50/90}$, 1/2 mg/L; 87.9% susceptible). In contrast, only 18.3% of MRSA strains were susceptible to levofloxacin, 32.4% to erythromycin, and 64.3% to clindamycin (Table 2).
- Against 466 β-haemolytic streptococci (including 189 *Streptococcus pyogenes* and 142 *S. agalactiae*), ceftaroline demonstrated greater activity ($MIC_{50/90}$, ≤0.008/0.015 mg/L) than penicillin ($MIC_{50/90}$, ≤0.03/0.06 mg/L). Decreased susceptibility was observed with tetracycline (42.9-43.3% susceptible), erythromycin (81.5% susceptible), clindamycin (91.8-92.1% susceptible) and levofloxacin (95.1-98.1% susceptible; Table 2).
- Ceftaroline was very active against viridans group streptococcal isolates (MIC_{50}, 0.03 mg/L and MIC_{90}, 0.06 mg/L). Using MIC_{90} results, ceftaroline was four-fold more active than penicillin ($MIC_{50/90}$, ≤0.03 mg/L and MIC_{90}, 0.25 mg/L) and eight-fold more active than ceftriaxone MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L) against this organism species (Table 2).
- Against all *E. coli* isolates, using USA-FDA breakpoints, 64.4% were susceptible to ceftaroline ($MIC_{50/90,}$ 0.25/>32 mg/L) which was slightly lower than ceftriaxone (71.9%, EUCAST breakpoints) and ceftazidime (74.0%, EUCAST breakpoints; Table 2). Among non-ESBL strains, 90.1% and 96.6% of strains were inhibited at ceftaroline MICs of ≤0.5 mg/L and ≤1 mg/L, respectively (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.5 mg/L; Table 1), while 102 ESBL-phenotype strains were markedly less susceptible to ceftaroline (MIC_{50}, >32 mg/L) and all other cephalosporins tested (data not shown).
- Ceftaroline was active against non-ESBL *Klebsiella pneumoniae* isolates with a MIC_{50} of 0.06 mg/L, MIC_{90} of 1 mg/L (Table 1) with 91.7% of strains inhibited at ≤1 mg/L (Table 1). In contrast, the majority of 61 ESBL-phenotype strains showed elevated ceftaroline MIC values (MIC_{50} and MIC_{90}, >32 mg/L; Table 1), and were less susceptible to all other cephalosporins tested (data not shown).

Conclusions

- Ceftaroline demonstrated broad-spectrum *in vitro* activity against the most common cSSSI pathogens isolated from patients in 54 medical centres in 19 European countries (including Israel and Turkey) and in South Africa during 2010.
- Activity of ceftaroline against MRSA/MSSA was similar to/four-fold greater than that of vancomycin and linezolid; activities against β-haemolytic and viridans group streptococci were similar to penicillin and ceftriaxone; activities against *E. coli* and *K. pneumoniae* were similar to ceftriaxone and ceftazidime.

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Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against the leading contemporary (2010) European and South African cSSSI pathogens

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
All *S. aureus* (1,455)					
Ceftaroline[b]	0.25	1	0.06 – 2	97.2 / -	- / -
Ceftriaxone[c]	4	>8	1 – >8	75.7 / 23.3	76.7 / 23.3
Cefuroxime	2	>16	≤0.12 – >16	76.7 / 23.3	76.7 / 23.3
Oxacillin	0.5	>2	≤0.25 – >2	76.7 / 23.3	76.7 / 23.3
Meropenem	≤0.12	8	≤0.12 – >8	76.7 / 23.3	76.7 / 23.3
Erythromycin	≤0.25	>4	≤0.25 – >4	73.7 / 25.6	73.7 / 25.9
Clindamycin	≤0.25	0.5	≤0.25 – >2	90.0 / 10.0	89.6 / 10.0
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	91.1 / 7.5	90.5 / 9.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	76.2 / 22.6	76.2 / 22.6
Moxifloxacin	≤0.5	4	≤0.5 – >4	77.1 / 17.7	77.1 / 17.7
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	98.8 / 1.2	98.8 / 1.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (339)					
Ceftaroline[b]	1	2	0.25 – 2	87.9 / -	- / -
Ceftriaxone[c]	>8	>8	4 – >8	0.0 / 100.0	0.0 / 100.0
Cefuroxime	>16	>16	1 – >16	0.0 / 100.0	0.0 / 100.0
Meropenem	4	>8	≤0.12 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>4	>4	≤0.25 – >4	32.4 / 66.7	32.4 / 67.0
Clindamycin	≤0.25	>2	≤0.25 – >2	64.3 / 35.7	64.0 / 35.7
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	79.6 / 17.1	79.1 / 20.4
Levofloxacin	>4	>4	≤0.5 – >4	18.3 / 78.8	18.3 / 78.8
Moxifloxacin	2	4	≤0.5 – >4	20.9 / 62.8	20.9 / 62.8
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	97.3 / 2.7	97.3 / 2.4
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (1,116)					
Ceftaroline[b]	0.25	0.25	0.06 – 0.5	100.0 / -	- / -
Ceftriaxone[c]	4	4	1 – >8	98.4 / 0.2	100.0 / 0.0
Cefuroxime	1	2	≤0.12 – 8	100.0 / 0.0	100.0 / 0.0
Meropenem	≤0.12	≤0.12	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	86.3 / 13.2	86.3 / 13.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.8 / 2.2	97.4 / 2.2
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	94.6 / 4.6	94.0 / 5.7
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	93.7 / 5.6	93.7 / 5.6
Moxifloxacin	≤0.5	≤0.5	≤0.5 – >4	94.2 / 3.9	94.2 / 3.9
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	99.3 / 0.7	99.3 / 0.5
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
β-hemolytic streptococci[e] (466)					
Ceftaroline[b]	≤0.008	0.015	≤0.008 – 0.06	- / -	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Penicillin	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Cefuroxime	≤0.12	≤0.12	≤0.12 – 0.5	- / -	100.0 / 0.0
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	4	≤0.25 – >4	81.5 / 17.4	81.5 / 17.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.8 / 7.9	92.1 / 7.9
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Tetracycline	8	>8	≤0.25 – >8	43.3 / 51.1	42.9 / 56.7
Levofloxacin	≤0.5	1	≤0.5 – >4	98.1 / 1.1	95.1 / 1.9
Moxifloxacin	≤0.5	≤0.5	≤0.5 – 2	- / -	98.5 / 1.1
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	- / -	98.9 / 1.1
Vancomycin	0.25	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Viridans group streptococci[f] (94)					
Ceftaroline[b]	0.03	0.06	≤0.008 – 0.5	- / -	- / -
Ceftriaxone[c]	0.25	0.5	≤0.06 – 8	96.8 / 2.1	93.6 / 6.4
Penicillin	≤0.03	0.25	≤0.03 – 2	81.9 / 0.0	90.4 / 0.0
Cefuroxime	0.25	1	≤0.12 – >16	- / -	86.2 / 13.8
Meropenem	≤0.12	0.25	≤0.12 – 4	97.9 / -	98.9 / 1.1
Erythromycin	≤0.25	>4	≤0.25 – >4	68.1 / 29.8	- / -
Clindamycin	≤0.25	>2	≤0.25 – >2	85.1 / 14.9	85.1 / 14.9
Linezolid	1	1	≤0.12 – 2	100.0 / -	- / -
Tetracycline	1	>8	≤0.25 – >8	59.6 / 37.2	- / -
Levofloxacin	1	2	≤0.5 – >4	93.6 / 5.3	- / -
Moxifloxacin	≤0.5	≤0.5	≤0.5 – 2	- / -	- / -
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	- / -	- / -
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Escherichia coli (334)					
Ceftaroline[b]	0.25	>32	0.015 – >32	64.4 / 31.1	- / -
Ceftriaxone[c]	≤0.06	>8	≤0.06 – >8	71.9 / 27.5	71.9 / 27.5
Ceftazidime	0.25	16	0.03 – >32	79.0 / 17.1	74.0 / 21.0
Cefuroxime	8	>16	1 – >16	66.1 / 28.2	66.1 / 33.9
Meropenem	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Ampicillin	>8	>8	≤1 – >8	29.6 / 70.4	- / 70.4
Ampicillin/sulbactam	16	>16	1 – >16	35.3 / 44.6	- / 64.7
Amoxicillin/clavulanate	8	>8	≤1 – >8	62.3 / 37.7	- / 37.7
Tetracycline	>8	>8	≤0.25 – >8	48.5 / 51.5	- / -
Gentamicin	≤1	>8	≤1 – >8	79.3 / 20.7	79.3 / 20.7
Ciprofloxacin	0.12	>4	≤0.03 – >4	58.4 / 41.0	58.1 / 41.6
Klebsiella pneumoniae (146)					
Ceftaroline[b]	0.5	>32	0.03 – >32	52.7 / 44.5	- / -
Ceftriaxone[c]	0.12	>8	≤0.06 – >8	61.6 / 38.4	61.6 / 38.4
Ceftazidime	0.25	>32	0.03 – >32	68.5 / 30.8	61.6 / 31.5
Cefuroxime	4	>16	≤2 – >16	58.9 / 37.7	58.9 / 41.1
Meropenem	≤0.12	0.5	≤0.12 – >8	95.9 / 3.4	96.6 / 2.1
Ampicillin/sulbactam	16	>32	2 – >32	45.9 / 46.6	- / 54.1
Amoxicillin/clavulanate	8	>8	≤1 – >8	57.5 / 42.5	- / 42.5
Tetracycline	2	>8	0.5 – >8	65.1 / 32.2	- / -
Gentamicin	≤1	>8	≤1 – >8	74.0 / 24.7	72.6 / 26.0
Ciprofloxacin	≤0.03	>4	≤0.03 – >4	69.2 / 28.8	67.1 / 30.8

a. Criteria as published by 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, 2010].
c. USA-FDA breakpoints were applied when available [Rocephin Product Insert, 2010].
d. Trimethoprim/sulfamethoxazole.
e. Includes: *Streptococcus dysgalactiae* (24 strains), *Streptococcus equisimilis* (2 strains), Group A *Streptococcus* (198 strains), Group B *Streptococcus* (142 strains), Group C *Streptococcus* (19 strains), Group F *Streptococcus* (4 strains), and Group G *Streptococcus* (77 strains).
f. Includes: *Streptococcus anginosus* (20 strains), *Streptococcus bovis* (3 strains), *Streptococcus canis* (1 strain), *Streptococcus constellatus* (11 strains), *Streptococcus equinus* (1 strain), *Streptococcus gallolyticus* (2 strains), *Streptococcus gordonii* (2 strains), *Streptococcus intermedius* (1 strain), *Streptococcus milleri* (3 strains), *Streptococcus mitis* (10 strains), *Streptococcus oralis* (5 strains), *Streptococcus parasanguinis* (1 strain), *Streptococcus porcinus* (1 strain), *Streptococcus salivarius* (1 strain), *Streptococcus sanguinis* (3 strains), *Streptococcus vestibularis* (3 strains), unspeciated alpha-haemolytic streptococci (6 strains), and unspeciated viridans group streptococci (20 strains).

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Table 1. Summary of ceftaroline activity tested against the leading contemporary (2010) European and South African cSSSI pathogens

Organism (n)	No. of organisms (cumulative %) inhibited at ceftaroline MIC (mg/L) of: ≤0.06	0.12	0.25	0.5	1	2	4	8	≥16	MIC_{50}	MIC_{90}
S. aureus (1455)	4 (0.3)	164 (11.6)	937 (76.0)	168 (87.5)	141 (97.2)	41 (100.0)	-	-	-	0.25	1
MRSA (339)	-	-	13 (3.8)	144 (46.3)	141 (87.9)	41 (100.0)	-	-	-	1	2
MSSA (1116)	4 (0.4)	164 (15.1)	924 (97.9)	24 (100.0)	-	-	-	-	-	0.25	0.25
BHS (466)	466 (100.0)	-	-	-	-	-	-	-	-	≤0.008	0.015
VGS (94)	88 (93.6)	1 (94.7)	4 (98.9)	1 (100.0)	-	-	-	-	-	0.03	0.06
EC-ESBL (102)	2 (2.0)	1 (2.9)	2 (4.9)	1 (5.9)	0 (5.9)	1 (6.9)	3 (9.8)	3 (12.8)	89 (100.0)	>32	>32
EC-non-ESBL (232)	97 (41.8)	63 (69.0)	24 (79.3)	25 (90.1)	15 (96.6)	2 (97.4)	2 (98.3)	2 (99.1)	2 (100.0)	0.12	0.5
KPN-ESBL (61)	-	2 (3.3)	0 (3.3)	0 (3.3)	1 (4.9)	1 (6.6)	1 (8.2)	1 (9.8)	55 (100)	>32	>32
KPN-non-ESBL (85)	43 (50.6)	20 (74.1)	7 (82.4)	5 (88.2)	3 (91.7)	5 (91.8)	1 (98.8)	1 (100.0)	-	0.06	1

BHS = β-hemolytic streptococci; VGS = viridans group streptococci; EC-ESBL = *E. coli* with ESBL phenotype; EC-non-ESBL = *E. coli* without an ESBL phenotype; KPN-ESBL = *K. pneumoniae* with ESBL phenotype; KPN-non-ESBL = *K. pneumoniae* without an ESBL phenotype