Spectrum and Potency of Ceftaroline Against Leading Pathogens Causing Community-acquired Respiratory Tract Infections in Europe and South Africa, 2010

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Abstract

Objective: Ceftaroline (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. The objective of this study was to determine the spectrum and potency of CPT against recent (2010) leading pathogens causing community-acquired respiratory tract infections (CA-RTI) isolated in Europe and South Africa (SAF).

Methods: A total of 1608 isolates from the 2010 Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Programme were identified as CA-RTI pathogens by the infection type and/or specimen type recorded by the submitter. Isolates were collected from patients in 53 medical centres in 19 European countries (including Israel and Turkey) and in South Africa (45 isolates, 1 medical centre) during 2010. Susceptibility testing for CPT and commonly used antimicrobials was performed by CLSI broth microdilution methodology. Susceptibility interpretations for comparators were as published in CLSI and EUCAST guidelines.

Results: The potencies of CPT against the leading pathogens isolated are shown in the Table. CPT was very active overall against *S. pneumoniae* (SPN; $MIC_{50/90}$, ≤0.008/0.12 mg/L) and inhibited 100.0% of all isolates at a MIC ≤0.5 mg/L. CPT was very potent against penicillin (PEN)-R and –intermediate (I) SPN ($MIC_{50/90}$, 0.12/25 and 0.03/0.12 mg/L, respectively) but potency was lower than seen against PEN-S isolates ($MIC_{50/90}$, ≤0.008/≤0.008 mg/L). CPT was also very active against 536 *Haemophilus influenzae* (HI) isolates with activity being slightly lower against beta-lactamase positive (BLP) isolates compared to BL negative (N) isolates. CPT also demonstrated good activity against 211 *Moraxella catarrhalis* isolates (MCAT; MIC_{90}, 0.12 mg/L).

Conclusions: This study demonstrated the potent *in vitro* activity of CPT against recent (2010) pathogens isolated from patients with documented CA-RTI from Europe and South Africa. These data suggest that ceftaroline fosamil could emerge as an important therapeutic option for CA-RTI in Europe and South Africa.

Introduction

Streptococcus pneumoniae, *Haemophilus influenzae* and *Moraxella catarrhalis* are the dominant bacterial pathogens causing community-acquired respiratory tract infections (CA-RTI). The emergence of multidrug-resistant *S. pneumoniae* (MDR-SPN) challenges the use of currently available β-lactams and agents from other antimicrobial classes.

Ceftaroline fosamil is the prodrug form of ceftaroline, a novel broad-spectrum cephalosporin with broad-spectrum *in vitro* bactericidal activity against Gram-positive organisms, including *S. pneumoniae* (including MDR-SPN) and methicillin-susceptible (MS) and –resistant (MR) *Staphylococcus aureus* (SA), as well as common Gram-negative organisms including *H. influenzae* and *M. catarrhalis*. In two phase 3 trials (NCT00509106; NCT00621504), ceftaroline fosamil was shown to be non-inferior to ceftriaxone for the treatment of patients with community-acquired bacterial pneumonia (CABP) requiring hospitalization. Ceftaroline fosamil has also been approved by the United States Food and Drug Administration (USA-FDA) for acute bacterial skin and skin structure infections.

In this study, we evaluated ceftaroline and comparator antimicrobial agents against 1,608 isolates from bacterial species associated with CA-RTIs collected in European and South African medical centres 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 1,608 isolates from the AWARE Programme were identified as CA-RTI pathogens by the infection type and/or specimen type recorded by the submitter. Isolates were collected from patients in 53 medical centres in 19 European countries (including Israel and Turkey) and South Africa (45 isolates, 1 medical centre) during 2010. European countries (number of centres) were: Belgium (1), Czech Republic (1), France (5), Germany (7), Greece (1), Hungary (1), Israel (1), Italy (6), Netherlands (1), Poland (2), Portugal (1), Romania (1), Russia (5), Slovenia (1), Spain (7), Sweden (2), Turkey (5), United Kingdom (4), Ukraine (1).

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). CLSI interpretations were based on M100-S22 and M45-A2 breakpoints. EUCAST breakpoints (2012) were also applied. USA-FDA breakpoints were applied for ceftaroline. *S. pneumoniae* were tested in Mueller-Hinton broth supplemented with 2.5–5% lysed horse blood, and *H. influenzae* were tested in Haemophilus Test Media, while *M. catarrhalis* isolates were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains assured proper test conditions were applied. These QC strains included *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247 and 49766. All QC results were within published ranges.

Results

- Ceftaroline was very active against *S. pneumoniae*, inhibiting all strains at ≤0.5 mg/L with 99.9% of isolates categorized as susceptible using the USA-FDA breakpoint of ≤0.25 mg/L (Table 1). Additionally, compared with other β-lactams tested, ceftaroline was the most active agent against *S. pneumoniae* (MIC_{90}, 0.12 mg/L; Table 2).
- The MIC range of ceftaroline was slightly lower against penicillin-susceptible *S. pneumoniae* (≤0.008 to 0.03 mg/L) than against penicillin-resistant strains (0.06–0.5 mg/L) (Tables 1 and 2).
- The activity of ceftaroline against penicillin-resistant *S. pneumoniae* (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L) was eight- and 16-fold greater than the activities of ceftriaxone (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) and amoxicillin/clavulanate (MIC_{50}, 2 mg/L and MIC_{90}, 8 mg/L), respectively (Table 2). Although the vast majority of all *S. pneumoniae* isolates were susceptible to ceftriaxone (94.3/81.5%, CLSI/EUCAST) and amoxicillin/clavulanate (92.0%, CLSI), non-susceptibility to these agents increased dramatically in the 149 penicillin-resistant isolates; for ceftriaxone 32.2/97.3% (CLSI/EUCAST) were non-susceptible, while for amoxicillin/clavulanate 45.0% were non-susceptible (26.2% resistant, CLSI).
- Overall erythromycin resistance against *S. pneumoniae* was 27.2% ranging from 9.5% in penicillin-susceptible strains to 75.2% in penicillin-resistant strains. Similarly, clindamycin/tetracycline/sulfamethoxazole-trimethoprim resistances ranged from 5.3/9.7/8.7% (CLSI) in penicillin-susceptible isolates to 53.7/59.7/61.7% in penicillin-resistant isolates. All isolates were susceptible to vancomycin and 99.0% were susceptible to levofloxacin (Table 2).
- Ceftaroline was highly active against *H. influenzae* (MIC_{50}, ≤0.008 mg/L and MIC_{90}, 0.015 mg/L; Table 2), with all strains inhibited at ≤0.5 mg/L of ceftaroline (Table 1). β-lactamase-producing *H. influenzae* strains (n=67, 12.5%) exhibited ceftaroline MIC values slightly higher (MIC_{50}, 0.015 mg/L and MIC_{90}, 0.06 mg/L) than those of non-β-lactamase-producing, ampicillin-susceptible strains (n=245; MIC_{50}, ≤0.008 mg/L and MIC_{90}, 0.015 mg/L (Table 1). Ceftaroline susceptibility was 99.8% overall using USA-FDA breakpoints (Table 2).
- The vast majority of *M. catarrhalis* strains exhibited elevated penicillin MIC values (β-lactamase-positive; data not shown). The highest ceftaroline MIC value for these organisms was only 0.5 mg/L (Table 1). Ceftaroline was the most active β-lactam agent tested against *M. catarrhalis* (MIC_{90}, 0.12 mg/L); it was 4- to 16-fold more active than ceftriaxone (MIC_{90}, 0.5 mg/L) or cefuroxime (MIC_{90}, 2 mg/L; Table 2).

Conclusions

- Ceftaroline, a novel parenteral cephalosporin, showed excellent *in vitro* activity against 1,608 contemporary (2010) CA-RTI pathogens from patients in Europe and South Africa and was the most active β-lactam agent tested against these pathogens.
- Ceftaroline demonstrated good *in vitro* activity against bacterial species frequently associated with contemporary respiratory tract infections in Europe and South Africa.

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Table 1. Summary of ceftaroline activity tested against contemporary (2010) European and South African CA-RTI pathogens

Organism/phenotype (no. tested)	No. of organisms (cumulative %) inhibited at ceftaroline MIC (mg/L) of: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
S. pneumoniae (861)	553 (64.2)	66 (71.9)	42 (76.8)	41 (81.5)	133 (97.0)	25 (99.9)	1 (100.0)	≤0.008	0.12
Penicillin-susceptible (600)[a]	550 (91.7)	44 (99.0)	6 (100.0)	-	-	-	-	≤0.008	≤0.008
Penicillin-intermediate (112)[a]	3 (2.7)	22 (22.3)	36 (54.5)	32 (83.0)	19 (100.0)	-	-	0.03	0.12
Penicillin-resistant (149)[a]	-	-	-	9 (6.0)	114 (82.6)	25 (99.3)	1 (100.0)	0.12	0.25
H. influenzae (536)	398 (74.3)	88 (90.7)	38 (97.8)	7 (99.1)	4 (99.8)	0 (99.8)	1 (100.0)	≤0.008	0.015
β-lactamase-negative (469)	382 (81.5)	65 (95.3)	20 (99.6)	1 (99.8)	1 (100.0)			≤0.008	0.015
β-lactamase-positive (67)	16 (23.9)	23 (58.2)	18 (85.1)	6 (94.0)	3 (98.5)	0 (98.5)	1 (100.0)	0.015	0.06
M. catarrhalis (211)	12 (5.7)	13 (11.9)	67 (43.6)	63 (73.5)	43 (93.8)	11 (99.1)	2 (100.0)	0.06	0.12

a. Criteria for S/I/R were according to CLSI oral penicillin V breakpoints (MIC, ≤0.06/0.12- 1/≥2 mg/L).

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against contemporary (2010) European and South African CA-RTI pathogens

Antimicrobial agent (no.tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Streptococcus pneumoniae (861)					
Ceftaroline[b]	≤0.008	0.12	≤0.008 – 0.5	99.9 / -	- / -
Penicillin[c]	≤0.03	2	≤0.03 – >4	93.5 / 0.1	- / -
Penicillin[d]	≤0.03	2	≤0.03 – >4	69.7 / 17.3	69.7 / 6.5
Amox/clav[e]	≤1	2	≤1 – >8	92.0 / 4.8	- / -
Ceftriaxone	≤0.06	1	≤0.06 – 4	94.3 / 0.6	81.5 / 0.6
Cefuroxime	≤0.12	4	≤0.12 – >16	79.0 / 19.7	78.0 / 21.0
Tetracycline	0.5	>8	≤0.25 – >8	74.2 / 25.0	74.0 / 25.8
TMP/SMX[f]	≤0.5	>4	≤0.5 – >4	69.6 / 21.8	75.5 / 21.8
Clindamycin	≤0.25	>1	≤0.25 – >1	81.3 / 18.0	82.0 / 18.0
Erythromycin	≤0.06	>8	≤0.06 – >8	72.7 / 27.2	72.7 / 27.2
Levofloxacin	1	1	≤0.5 – >4	99.0 / 1.0	99.0 / 1.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-susceptible *S. pneumoniae* (600)					
Ceftaroline[b]	≤0.008	≤0.008	≤0.008 – 0.03	100.0 / -	- / -
Penicillin[c]	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / 0.0	- / -
Penicillin[d]	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / 0.0	100.0 / 0.0
Amox/clav[e]	≤1	≤1	≤1 – >8	99.7 / 0.3	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 1	100.0 / 0.0	99.8 / 0.0
Cefuroxime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	4	≤0.25 – >8	89.3 / 9.7	89.3 / 10.7
TMP/SMX[f]	≤0.5	2	≤0.5 – >4	85.3 / 8.7	89.2 / 8.7
Clindamycin	≤0.25	≤0.25	≤0.25 – >1	94.3 / 5.3	94.7 / 5.3
Erythromycin	≤0.06	0.12	≤0.06 – >8	90.3 / 9.5	90.3 / 9.5
Levofloxacin	1	1	≤0.5 – >4	99.5 / 0.5	99.5 / 0.5
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-intermediate *S. pneumoniae* (112)					
Ceftaroline[b]	0.03	0.12	≤0.008 – 0.12	100.0 / -	- / -
Penicillin[c]	0.25	1	0.12 – 1	100.0 / 0.0	- / -
Penicillin[d]	0.25	1	0.12 – 1	0.0 / 0.0	0.0 / 0.0
Amox/clav[e]	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Ceftriaxone	0.25	1	≤0.06 – 2	99.1 / 0.0	88.4 / 0.0
Cefuroxime	0.5	4	≤0.12 – 4	71.4 / 19.6	64.3 / 28.6
Tetracycline	>8	>8	≤0.25 – >8	39.3 / 60.7	37.5 / 60.7
TMP/SMX[f]	1	>4	≤0.5 – >4	46.4 / 39.3	56.3 / 39.3
Clindamycin	≤0.25	>1	≤0.25 – >1	59.8 / 38.4	61.6 / 38.4
Erythromycin	2	>8	≤0.06 – >8	42.0 / 58.0	42.0 / 58.0
Levofloxacin	1	1	≤0.5 – >4	98.2 / 1.8	98.2 / 1.8
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0

Antimicrobial agent (no.tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Penicillin-resistant *S. pneumoniae* (149)					
Ceftaroline[b]	0.12	0.25	0.06 – 0.5	99.3 / -	- / -
Penicillin[c]	2	4	2 – >4	62.4 / 0.7	- / -
Penicillin[d]	2	4	2 – >4	0.0 / 100.0	0.0 / 37.6
Amox/clav[e]	2	8	≤1 – 8	55.0 / 26.2	- / -
Ceftriaxone	1	2	0.5 – 4	67.8 / 3.4	2.7 / 3.4
Cefuroxime	8	16	2 – >16	0.0 / 99.3	0.0 / 100.0
Tetracycline	>8	>8	≤0.25 – >8	39.6 / 59.7	39.6 / 60.4
TMP/SMX[f]	4	>4	≤0.5 – >4	23.5 / 61.7	34.9 / 61.7
Clindamycin	>1	>1	≤0.25 – >1	45.0 / 53.7	46.3 / 53.7
Erythromycin	>8	>8	≤0.06 – >8	24.8 / 75.2	24.8 / 75.2
Levofloxacin	1	1	≤0.5 – >4	97.3 / 2.7	97.3 / 2.7
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Haemophilus influenzae (536)					
Ceftaroline[b]	≤0.008	0.015	≤0.008 – 0.5	99.8 / -	- / -
Ampicillin	≤1	8	≤1 – >8	86.8 / 11.6	86.8 / 13.2
Amox/clav[e]	≤1	≤1	≤1 – 4	100.0 / 0.0	90.9 / 9.1
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / -	99.8 / 0.2
Cefuroxime	0.5	2	≤0.12 – >16	99.1 / 0.4	79.1 / 6.0
Tetracycline	0.5	1	≤0.25 – >8	98.9 / 1.1	98.3 / 1.1
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.8 / -	99.8 / 0.2
Moraxella catarrhalis (211)					
Ceftaroline[b]	0.12	0.12	≤0.008 – 0.5	- / -	- / -
Ceftriaxone	0.25	0.5	≤0.06 – 2	100.0 / -	99.5 / 0.0
Cefuroxime	1	2	0.25 – 4	100.0 / 0.0	76.3 / 0.9
Penicillin	>4	>4	≤0.03 – >4	- / -	- / -
Amox/clav[e]	≤1	≤1	≤1	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
TMP/SMX[f]	≤0.5	≤0.5	≤0.5 – 4	96.7 / 0.5	96.7 / 2.8
Erythromycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	97.2 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied when available [Teflaro Product Insert, 2010].
c. Criteria as published by CLSI [2012] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by CLSI [2012] for 'Penicillin (oral penicillin V)'.
e. Amoxicillin/clavulanate.
f. Trimethoprim/sulfamethoxazole.