Antimicrobial Activity of Ceftaroline and Comparator Agents Against Contemporary (2010) *Staphylococcus aureus* Isolates from Europe and South Africa

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Abstract

Objective: To determine the activity of ceftaroline (CPT), the active metabolite of the prodrug ceftaroline fosamil, and comparator agents tested against recent (2010) *S. aureus* (SA) isolated in Europe (EU) and South Africa (SAF). CPT is a novel cephalosporin exhibiting broad-spectrum *in vitro* bactericidal activity against Gram-positive organisms including methicillin-susceptible (MS) and resistant (MR) SA, as well as many common Gram-negative pathogens.

Methods: Susceptibility testing for CPT and commonly used antimicrobials was performed by the CLSI broth microdilution methodology on a total of 3,598 isolates from the 2010 Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Programme. Susceptibility interpretations for the comparators were as published in CLSI and EUCAST guidelines. Isolates were collected from patients in 57 medical centres in 19 EU countries, including Israel and Turkey, and in SAF (1 medical centre).

Results: CPT was very active ($MIC_{50/90}$, 0.25/1 mg/L) and inhibited >99.9% of all 3,598 isolates at a MIC of ≤2 mg/L (see Table 1). CPT showed potent activity against MRSA ($MIC_{50/90}$, 1/2 mg/L overall) but lower than seen against MSSA ($MIC_{50/90}$, 0.25/0.25 mg/L overall). Only one strain (0.03%) demonstrated a CPT MIC value of >2 mg/L; the single isolate was from Spain with a CPT MIC value of 8 mg/L. Resistance (EUCAST) to several common-use antimicrobial agents was moderate; oxacillin/levofloxacin/erythromycin/ clindamycin/ tetracycline resistance, respectively, by region was: EU 25.4/24.9/26.4/11.2/9.7%, and SAF 28.3/30.4/30.4/23.9/15.2%.

Conclusions: This study demonstrated the potent *in vitro* activity of CPT tested against recent (2010) SA isolates, including MRSA strains in EU and SAF. Resistance to many commonly used antimicrobial agents was moderate with variability observed between geographical regions. These data suggest that ceftaroline fosamil could emerge as an important therapy for infections caused by SA, including MRSA, in EU and SAF.

Introduction

β-lactam agents bind to penicillin binding proteins (PBPs) in the cell wall and inhibit transpeptidase activity with resulting cell death. Methicillin, a penicillinase stable agent, was introduced into clinical practice in 1959; however resistance to this agent was reported within 2 years and methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major therapeutic problem to date. MRSA arises by the horizontal acquisition of PBP2a (a modified PBP) encoded by the *mecA* gene resulting in decreased binding affinity of methicillin to this modified PBP.

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil (an N-phosphonoamino water-soluble cephalosporin) has demonstrated *in vitro* activity against typical acute skin and skin structure infection (ABSSSI) pathogens, including MRSA, streptococci, and common enteric Gram-negative bacilli such as non-extended spectrum β-lactamase (non-ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*. Ceftaroline, in contrast to other β-lactams, has been shown to have a high affinity for PBP2a in MRSA. In two Phase 3 trials (NCT00424190; NCT00423657), ceftaroline was found to be non-inferior to vancomycin plus aztreonam for the treatment of patients with cSSSI. Ceftaroline was approved in 2010 by the United States Food and Drug Administration (USA-FDA) for the treatment of ABSSSI and community-acquired bacterial pneumonia.

In this study, we evaluated ceftaroline and comparator antimicrobial agents tested against *S. aureus* collected in European and South African hospitals during 2010 as part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Programme, a global ceftaroline resistance surveillance study.

Materials and Methods

Organism Collection: A total of 3,598 *S. aureus* isolates were tested. These isolates were collected from patients in 57 medical centres in 19 European countries, including Israel and Turkey, and in South Africa (1 medical centre) during the 2010 AWARE Programme. European countries (number of centres) were: Belgium (1), Czech Republic (1), France (5), Germany (7), Greece (2), Hungary (1), Israel (1), Italy (7), Netherlands (1), Poland (2), Portugal (1), Romania (1), Russia (5), Slovenia (1), Spain (7), Sweden (2), Turkey (5), United Kingdom (5), 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). Isolates were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). USA-FDA breakpoints for ceftaroline and ceftriaxone were used in the absence of CLSI / EUCAST interpretative criteria. Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. QC strains included *S. aureus* ATCC 29213. All QC results were within published ranges.

Results

- Overall, and for Europe and South Africa individually, ceftaroline exhibited excellent activity against methicillin-susceptible *S. aureus* (MSSA) isolates (MIC_{50} and MIC_{90}, both 0.25 mg/L). The highest ceftaroline MIC result observed among MSSA was 1 mg/L (Table 1).
- Ceftaroline was eight-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, both 4 mg/L) when tested against MSSA. Erythromycin resistance was 12.7/13.1% (CLSI/EUCAST) while all other tested agents were ≥93.8% susceptible when tested against MSSA (Table 2).
- Ceftaroline demonstrated activity against MRSA from both Europe and South Africa, inhibiting 99.9% of all 916 isolates at a MIC ≤2 mg/L (Table 1). Ceftaroline was at least equally active (MIC_{90} results) to linezolid and vancomycin versus all *S. aureus* (Table 2). Only one MRSA isolate (from Spain) had a ceftaroline MIC of >2 mg/L (Table 1).
- The most active agents applying CLSI interpretive criteria against MRSA were: trimethoprim/ sulfamethoxazole, ($MIC_{50/90}$, ≤0.5/≤0.5 mg/L; 97.3% susceptible), 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; 86.1% susceptible). In contrast, only 15.0% of MRSA strains were susceptible to levofloxacin, 32.9% to erythromycin, 62.4% to clindamycin and 77.6% to tetracycline (Table 2).
- Against all isolates, resistance (EUCAST) to several common-use antimicrobial agents was moderate and varied between regions; oxacillin/ levofloxacin/erythromycin/clindamycin/tetracycline resistance, respectively, was: Europe 25.4/24.9/26.4/11.2/9.7%, and South Africa 28.3/30.4/30.4/23.9/15.2%.

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against contemporary (2010) European and South African *S. aureus*

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
All *S. aureus* (3,598)					
Ceftaroline[b]	0.25	1	0.03 – 8	96.5 / -	- / -
Ceftriaxone[c]	4	>8	≤0.06 – >8	73.7 / 25.5	74.5 / 25.5
Cefuroxime	2	>16	≤0.12 – >16	74.5 / 25.5	74.5 / 25.5
Oxacillin	0.5	>2	≤0.25 – >2	74.5 / 25.5	74.5 / 25.5
Meropenem	≤0.12	>8	≤0.12 – >8	74.5 / 25.5	74.5 / 25.5
Erythromycin	≤0.25	>4	≤0.25 – >4	72.8 / 26.0	72.8 / 26.4
Clindamycin	≤0.25	>2	≤0.25 – >2	88.6 / 11.2	88.3 / 11.4
Linezolid	1	1	≤0.12 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	2	≤0.25 – >8	90.4 / 8.6	89.7 / 9.8
Levofloxacin	≤0.5	>4	≤0.5 – >4	73.7 / 25.0	73.7 / 25.0
Moxifloxacin	≤0.5	4	≤0.5 – >4	74.6 / 19.8	74.6 / 19.8
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	98.9 / 1.1	98.9 / 0.9
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (916)					
Ceftaroline[b]	1	2	0.12 – 8	86.1 / -	- / -
Ceftriaxone[c]	>8	>8	≤0.06 – >8	0.0 / 100.0	0.0 / 100.0
Cefuroxime	>16	>16	1 – >16	0.0 / 100.0	0.0 / 100.0
Meropenem	8	>8	≤0.12 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>4	>4	≤0.25 – >4	32.9 / 65.1	32.9 / 65.5
Clindamycin	≤0.25	>2	≤0.25 – >2	62.4 / 37.6	62.3 / 37.6
Linezolid	1	1	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	77.6 / 19.9	76.9 / 22.4
Levofloxacin	>4	>4	≤0.5 – >4	15.0 / 82.0	15.0 / 82.0
Moxifloxacin	2	4	≤0.5 – >4	17.6 / 65.3	17.6 / 65.3
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	97.3 / 2.7	97.3 / 2.5
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (2,682)					
Ceftaroline[b]	0.25	0.25	0.03 – 1	100.0 / -	- / -
Ceftriaxone[c]	4	4	1 – >8	98.4 / 0.1	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	86.5 / 12.7	86.5 / 13.1
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.6 / 2.2	97.2 / 2.4
Linezolid	1	2	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	94.7 / 4.8	94.1 / 5.5
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	93.8 / 5.5	93.8 / 5.5
Moxifloxacin	≤0.5	≤0.5	≤0.5 – >4	94.1 / 4.3	94.1 / 4.3
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	99.5 / 0.5	99.5 / 0.3
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the 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.

Conclusions

- Ceftaroline demonstrated potent activity against *S. aureus* (MSSA and MRSA) collected from patients in 57 medical centres in 19 European countries, including Israel and Turkey, and in South Africa (one medical centre) during the 2010 AWARE Programme.
- Resistance to many commonly used antimicrobial agents was high among MRSA and moderate overall with variability observed between Europe and South Africa.

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Table 1. Summary of ceftaroline activity tested against contemporary (2010) European and South African *S. aureus*

Region/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	MIC_{50}	MIC_{90}
All isolates										
S. aureus (3598)	13 (0.4)	420 (12.0)	2220 (73.7)	404 (85.0)	414 (96.5)	126 (>99.9)	0 (>99.9)	1 (100.0)	0.25	1
MRSA (916)	-	1 (0.1)	30 (3.4)	345 (41.0)	413 (86.1)	126 (99.9)	0 (99.9)	1 (100.0)	1	2
MSSA (2682)	13 (0.5)	419 (16.1)	2190 (97.8)	59 (>99.9)	1 (100.0)	-	-	-	0.25	0.25
Europe										
S. aureus (3552)	13 (0.4)	417 (12.1)	2190 (73.8)	404 (85.1)	408 (96.6)	119 (>99.9)	0 (>99.9)	1 (100.0)	0.25	1
MRSA (903)	-	1 (0.1)	30 (3.4)	345 (41.6)	407 (86.7)	119 (99.9)	0 (99.9)	1 (100.0)	1	2
MSSA (2649)	13 (0.5)	416 (16.2)	2160 (97.7)	59 (>99.9)	1 (100.0)	-	-	-	0.25	0.25
South Africa										
S. aureus (46)	-	3 (6.5)	30 (71.7)	0 (71.7)	6 (84.8)	7 (100.0)	-	-	0.25	2
MRSA (13)	-	-	-	-	6 (46.2)	7 (100.0)	-	-	2	2
MSSA (33)	-	3 (9.1)	30 (100.0)	-	-	-	-	-	0.25	0.25