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Ceftaroline and Comparator Agent Activity Against Contemporary (2010) *Staphylococcus aureus* Isolates from Asia-Pacific Region and South Africa Hospitals

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Amended Abstract

Background: Ceftaroline (CPT) is a novel, parenteral cephalosporin with broad-spectrum activity including potent, bactericidal activity against methicillin-susceptible (MS) and -resistant (MR) *S. aureus* (SA). CPT fosamil is approved by the USA-FDA for treatment of acute bacterial skin and skin structure infections (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 1,080 SA isolates collected in 2010 from 25 medical centers located in 7 Asia-Pacific (APAC) countries and South Africa (SAF).

Results: Isolates were collected mostly from ABSSSI (57.8%), respiratory infections (21.5%) and bacteremia (16.5%), and distributed among the 8 countries as defined in Table 1. Against the 1,080 SA isolates, CPT was very active ($MIC_{50/90}$, 0.25/1 µg/ml) with only a 4- to 8-fold MIC increase among MRSA ($MIC_{50/90}$, 1/2 µg/ml) compared to MSSA ($MIC_{50/90}$, 0.25 µg/ml). CPT MICs were similar among countries except for a lower MIC_{90} in Australia (AUS). Highest observed CPT MIC results were 4 and 8 µg/ml, all from Thailand (THAI). MRSA rates by country varied greatly from Singapore (71.2%), Korea (51.4%), THAI (47.2%), Hong Kong (44.7%), China (42.0%) to SAF, AUS, Malaysia (22-28%). Clindamycin-R varied from 0.0% in Malaysia to 50.0% in THAI. All SA were S to vancomycin, linezolid and daptomycin.

Conclusions: Against recent SA isolates collected from serious infections in the APAC region, CPT demonstrated potent *in vitro* activity. CPT was consistently active, while MRSA rates and other resistances varied greatly by country within this region.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of healthcare-associated infections and a major problem in hospitals and intensive-care units (ICUs) worldwide. MRSA is associated with a wide range of infections, including acute bacterial skin and skin-structure infections (ABSSSIs), respiratory tract infections, bacteremia, endocarditis, osteomyelitis, prosthetic joint infections, and catheter-related infections. The past decade has seen an increase in the incidence of MRSA in many hospital settings and the emergence of community-acquired MRSA (CA-MRSA).

Ceftaroline, the active form of the prodrug ceftaroline fosamil, is a cephalosporin with *in vitro* bactericidal activity against Gram-positive organisms, including MRSA and common Gram-negative pathogens. Ceftaroline fosamil is approved by the United States Food and Drug Administration (USA-FDA) for the treatment of ABSSSI (including due to MRSA) and community-acquired bacterial pneumonia (CABP) excluding cases due to MRSA. In the present study, we evaluated the activity of ceftaroline tested against *S. aureus* from the Asia-Pacific (APAC) region and South Africa hospitals in 2010.

Materials and Methods

Organism collection: A total of 1,080 nonduplicate isolates of *S. aureus* collected in 2010 from 25 medical centers located in 7 APAC countries and South Africa were evaluated. The isolates were collected mostly from ABSSSI (57.8%), respiratory tract infections (21.5%) and bacteremias (16.5%) as part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance program.

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 used to treat *S. aureus* infections. Validated MIC panels were manufactured by ThermoFisher Scientific, Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). The isolates were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). 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 documents (M100-S22) and EUCAST (2012). USA-FDA interpretive criteria for ceftaroline susceptibility were used.

Results

- *S. aureus* was very susceptible to ceftaroline ($MIC_{50/90}$, 0.25/1 µg/ml) overall and ceftaroline MIC values were similar among countries except for a lower MIC_{90} in Australia (Table 1).
- When tested against methicillin (oxacillin) -susceptible strains (MSSA), ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/ml) was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 µg/ml) and eight-fold more active than linezolid (MIC_{50} and MIC_{90}, 2 µg/ml; Table 2).
- The highest ceftaroline MIC value among MSSA strains was only 1 µg/ml (one isolate [0.1%]) and 95.8% of strains were inhibited at a ceftaroline MIC of ≤0.25 µg/ml (Table 1).
- Ceftaroline MIC values ranged from 0.25 to 8 µg/ml (MIC_{50}, 1 µg/ml and MIC_{90}, 2 µg/ml) when tested against MRSA. All but 3 isolates were inhibited at a ceftaroline MIC of ≤2 µg/ml and 74.4% were inhibited at ceftaroline MIC of ≤1 µg/ml (Tables 1 and 2). Three isolates (0.7% of MRSA) from the same medical center in Thailand had ceftaroline MIC values >2 µg/ml (Table 1).
- Although ceftaroline MIC values were slightly higher (approximately four-fold) among MRSA compared to MSSA, its activity was considerably greater than other cephalosporins and carbapenems tested against MRSA (data not shown). Ceftaroline activity was comparable to that of linezolid ($MIC_{50/90}$, 1/2 µg/ml) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/ml) and slightly lower than daptomycin (MIC_{50}, 0.25 µg/ml and MIC_{90} 0.5 µg/ml) and tigecycline (MIC_{50} 0.12 µg/ml and MIC_{90} 0.25 µg/ml) when tested against MRSA strains (Table 2).

Table 1. *Summary of Ceftaroline Activity Against S. aureus from Medical Centers Located in the APAC Region and South Africa (2010).*

Organism (no. tested)	No. of isolates at ceftaroline MIC (µg/ml) of: ≤0.06	0.12	0.25	0.5	1	2	4	8	MIC_{50}	MIC_{90}
S. aureus (1,080)	2	80	567	166	161	101	2	1	0.25	1
MSSA (673)	2	80	563	27	1				0.25	0.25
MRSA (407)	0	0	4	139	160	101	2	1	1	2
Australia (466)	1	51	273	97	39	5			0.25	0.5
China (327)	0	11	171	30	57	58			0.25	2
Hong Kong (38)	0	4	19	5	7	3			0.25	1
Korea (74)	1	4	30	11	8	20			0.5	2
Malaysia (27)	0	2	18	1	6				0.25	1
Singapore (66)	0	2	11	21	31	1			0.5	1
South Africa (46)	0	3	30	0	6	7			0.25	2
Thailand (36)	0	3	15	1	7	7	2	1	0.25	2

Table 2. *Activity of Ceftaroline and Comparator Antimicrobial Agents when Tested against 1,080 S. aureus Isolates Collected from Medical Centers Located in the APAC Region and South Africa (2010).*

Organism/Antimicrobial agent (no. tested)	MIC (µg/ml) MIC_{50}	MIC_{90}	Range	%S / %R CLSI[a]	EUCAST[a]
S. aureus (all; 1,080)					
Ceftaroline[b]	0.25	1	0.03 – 8	90.4 / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	62.3 / 37.7	62.3 / 37.7
Ceftriaxone	4	>8	0.25 – >8	62.3 / 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
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	68.3 / 31.2	68.3 / 31.2
TMP/SMX[d]	≤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[b]	0.25	0.25	0.03 – 1	100.0 / -	- / -
Ceftriaxone	4	4	0.25 – 8	100.0 / 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
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	93.8 / 5.9	93.8 / 5.9
TMP/SMX[d]	≤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[b]	1	2	0.25 – 8	74.4 / -	- / -
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
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Levofloxacin	>4	>4	≤0.5 – >4	26.3 / 73.0	26.3 / 73.0
TMP/SMX[d]	≤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

a. Criteria as published by the CLSI [2012] and EUCAST [2011], ß-lactam susceptibility should be directed by the oxacillin test results.
b. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Teflaro® Prescribing Information, 2012].
c. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Tygacil® Prescribing Information, 2011].
d. TMP/SMX = trimethoprim/sulfamethoxazole.

- MRSA strains exhibited high rates of resistance to erythromycin (70.8% and 72.0% according to CLSI and EUCAST breakpoint criteria, respectively), levofloxacin (73.0%), tetracycline (57.7% and 58.2% according to CLSI and EUCAST breakpoint criteria, respectively) and clindamycin (50.6%; Table 2).
- MRSA rates by country varied greatly. The highest rate was observed in Singapore (71.2%), followed by Korea (51.4%), Thailand (47.2%), Hong Kong (44.7%), China (42.2%), South Africa (28.3%), Australia (28.1%) and Malaysia (22.2%; Table 3).
- Clindamycin resistance varied from 0.0% in Malaysia to 50.0% in Thailand, and resistance to trimethoprim/sulfamethoxazole was highest in Singapore (22.7%) and Malaysia (22.2%). All *S. aureus* were susceptible to vancomycin, linezolid and daptomycin and tigecycline (Tables 2 and 3).

Table 3. *Susceptibility Rates for Ceftaroline and Comparator Agents Stratified by Nation.*

Antimicrobial agents (no. tested)	% susceptible / %resistant[a] (no. of strains) Australia (466)	China (327)	Hong Kong (38)	Korea (74)	Malaysia (27)	Singapore (66)	South Africa (46)	Thailand (36)
Ceftaroline[b]	98.9 / -	82.3 / -	92.1 / -	73.0 / -	100.0 / -	98.5 / -	84.8 / -	72.2 / -
Oxacillin	71.9 / 28.1	57.8 / 42.2	55.3 / 44.7	48.6 / 51.4	77.8 / 22.2	28.8 / 71.2	71.7 / 28.3	52.8 / 47.2
Erythromycin	76.6 / 23.2	36.7 / 62.1	47.4 / 52.6	45.9 / 54.1	77.8 / 11.1	30.3 / 66.7	69.6 / 28.3	47.2 / 52.8
Clindamycin	90.6 / 9.4	53.8 / 46.2	71.1 / 28.9	68.9 / 31.1	100.0 / 0.0	75.8 / 24.2	76.1 / 23.9	50.0 / 50.0
Levofloxacin	85.9 / 13.9	54.4 / 45.0	60.5 / 36.8	66.2 / 33.8	77.8 / 22.2	25.8 / 72.7	69.6 / 30.4	50.0 / 50.0
Linezolid	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0
Tetracycline	90.8 / 9.2	48.6 / 50.8	52.6 / 47.4	67.6 / 32.4	59.3 / 40.7	50.0 / 50.0	84.8 / 13.0	50.0 / 50.0
TMP/SMX[c]	90.1 / 9.9	92.0 / 8.0	86.8 / 13.2	98.6 / 1.4	77.8 / 22.2	77.3 / 22.7	91.3 / 8.7	91.3 / 8.7
Tigecycline[d]	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -
Vancomycin	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0
Daptomycin	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -

a. According to CLSI breakpoint criteria unless noted [CLSI, 2012].
b. USA-FDA breakpoint criteria were applied [Teflaro® Prescribing Information, 2012].
c. TMP/SMX = trimethoprim/sulfamethoxazole.
d. USA-FDA breakpoints were applied [Tygacil® Prescribing Information, 2011].

Conclusions

- Ceftaroline demonstrated potent *in vitro* activity against recent *S. aureus* isolates collected from serious infections in the APAC region and South Africa in 2010.
- Ceftaroline exhibited *in vitro* activity most similar to those of daptomycin, linezolid, tigecycline and vancomycin.
- Ceftaroline was consistently active, while MRSA rates and other resistances varied greatly by the nations within this region.

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