Activity of Ceftaroline Tested against Methicillin-resistant *Staphylococcus aureus* Clones from Australia and New Zealand (2010)

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Abstract

Objective: To evaluate the activity of ceftaroline (CPT) against methicillin-resistant *Staphylococcus aureus* (MRSA) clones isolated from patients in Australia (AUS) and New Zealand (NZ). 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 MRSA. We evaluated the activity of CPT against MRSA clones isolated from patients in AUS and NZ.

Methods: Susceptibility testing for CPT and comparator antimicrobials was performed using CLSI broth microdilution methods on 141 isolates obtained from AUS (n=131) and NZ (n=10) as part of the SENTRY Programme, Asia Pacific Region (2010). Isolates were assigned to their clonal complex (CC) using a novel HRM SNP typing assay (Minim typing).

Results: Hospital-associated clones (CC8 and CC22) accounted for 48% of all MRSA isolates examined. CPT demonstrated good activity against all MRSA CC's. CPT MIC_{90} values (0.5 mg/L) were lower for MRSA strains with community-associated clonal complexes (CC93, CC1, CC30, CC5, and CC88). Resistance to mupirocin, tetracycline, gentamicin, fusidic acid, erythromycin, or cotrimoxazole did not affect CPT activity against MRSA isolates (overall MIC_{90}, 1 mg/L; range 0.5-2 mg/L by CC). No vancomycin-intermediate or -resistant strains were detected.

Conclusion: CPT exhibited potent activity against MRSA isolates and commonly circulating clonal complexes from AUS and NZ, in both community and hospital settings. All community-associated isolates had both MIC_{50} and MIC_{90} of 0.5 mg/L. Compared to community-associated MRSA clones, some hospital clones had slightly higher CPT MIC values, especially CC8 (MIC_{90}, 2 mg/L).

Introduction

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a novel cephalosporin exhibiting broad-spectrum *in vitro* bactericidal activity against both Gram-negative and Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). We hypothesized that community-associated strains of MRSA would have a different ceftaroline MIC distribution to hospital-associated strains, as observed with other β-lactams.

Materials and Methods

Isolates

S. aureus isolates from the SENTRY Antimicrobial Surveillance Programme (Australia [six medical centres from six states] and New Zealand [two medical centres]) collected during 2010 were analysed. Isolates were collected from inpatients with bacteraemia, pneumonia, complicated skin and skin-structure infections, and other infections.

Susceptibility testing

Susceptibility testing for ceftaroline and comparator antimicrobials was performed using custom-made dry-form broth microdilution panels prepared by ThermoFisher Scientific (formerly Trek Diagnostic Systems, Inc.), according to Clinical and Laboratory Standards Institute (CLSI) standards, and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). Isolates with an oxacillin MIC at >2 mg/L and *mecA* positive were selected for further analysis.

Methods-continued

High Resolution Melt SNP typing assay (Minim)

The Minim assay is a multi-locus sequence typing (MLST) based *S. aureus* typing scheme that uses high resolution melting analysis of single nucleotide polymorphism (SNP)-nucleated PCR fragments. Six targets were amplified (arcC, gmk, aroE, pta, tpi36, tpi241) using a real-time PCR platform (Roche LightCycler® 480 II system) with LightCycler® 480 High Resolution Melting Master (Roche), using 10 µl reaction volume. Theoretical melt curves from the known sequences of each target was calculated and assigned a unique number. A complete combination of all six targets melted corresponds to an allelic profile, or melt curve number (MelT).

Assignment to Clonal Complex

A MelT key was used to convert the MelT number into a clonal complex (CC).

Results

- Hospital-associated clones (CC8 and CC22) accounted for 48% of all MRSA isolates examined (Figure 1).
- The proportion of different CC by country is shown in Figure 2.
- Ceftaroline demonstrated good activity against all MRSA CCs (Table 1). Ceftaroline MIC_{90} values (0.5 mg/L) were lower for MRSA strains with community-associated CCs (CC93, CC1, CC30, CC5, and CC88).
- CC22 MICs were similar to those of community-associated strains.
- Resistance to mupirocin, tetracycline, gentamicin, fusidic acid, erythromycin, or cotrimoxazole did not adversely affect ceftaroline activity against MRSA isolates (overall MIC_{90}, 1 mg/L; range, 0.5-2 mg/L by CC).
- Multi-drug resistance was rare amongst community-associated CCs, but was seen in the majority of hospital-associated CCs.
- The different CCs show distinct resistance profiles (Table 2). Two strains in CC8 with none or one additional resistance probably represent community-associated strains, rather than the dominant multi-resistant sequence type ST239 from CC8.
- No vancomycin-intermediate or -resistant strains were detected.

Figure 1. Distribution of clonal complexes

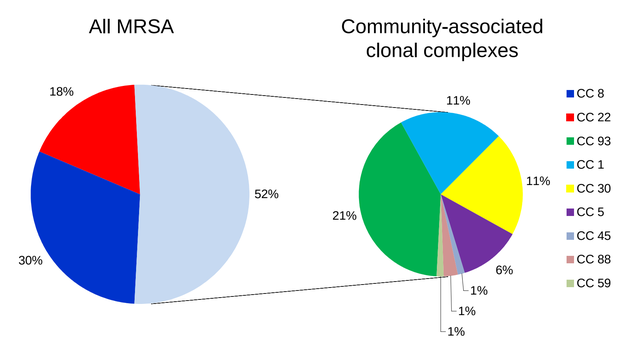

Figure 2. Clonal complexes by country

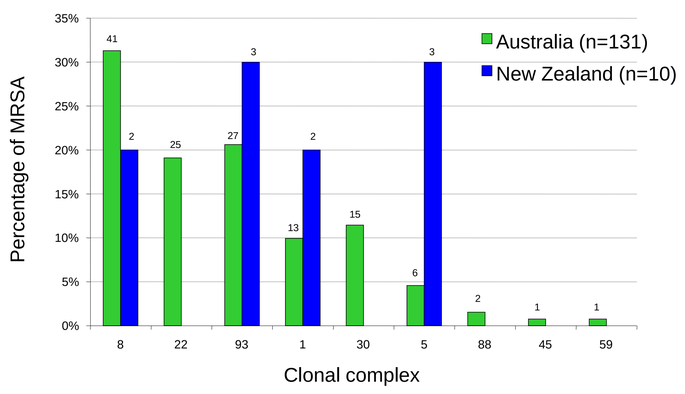

Table 1. Ceftaroline MIC distribution by clonal complex

Clonal complex (no. tested)	Ceftaroline MIC (mg/L) 0.25	0.5	1	2	MIC_{50}	MIC_{90}
Hospital-associated						
8 (43)		4	34	5	1	2
22 (25)		21	4		0.5	1
Community-associated						
93 (30)	1	29			0.5	0.5
1 (15)		15			0.5	0.5
30 (15)		14	1		0.5	0.5
5 (9)	2	7			0.5	-
88 (2)		2			0.5	-
45 (1)		1			0.5	-
59 (1)		1			0.5	-
All (141)	3	94	39	5	0.5	1

Table 2. Clonal complex versus resistance profile

	HA[a]		Community-associated							
Resistance profile[b]	8[c]	22	93	1	30	5	45	88	59	Total
[d]	1		29	10	14	5		1		60
Fus				3		2				5
Tet					1					1
Cip		6					1			7
Ery	1		1	1		2		1	1	7
Ery Fus				1						1
Ery Gen	1									1
Ery Tet	1									1
Ery TetGen	7									7
EryCip	1	19								20
EryCip Gen	1									1
EryCipTet	1									1
EryCipTetGen	28									28
EryCipTetGenFus	1									1
	43	25	30	15	15	9	1	2	1	141

a. HA = hospital-associated.
b. Ery, erythromycin-resistant; Cip, ciprofloxacin-resistant; Tet, tetracycline-resistant; Gen, gentamicin-resistant; Fus, fusidic acid-resistant.
c. May include a small number of community-associated strains.
d. no additional resistances detected.

Conclusions

- Ceftaroline exhibited potent *in vitro* activity against MRSA isolates and commonly circulating clonal complexes from Australia and New Zealand in both community and hospital settings.
- All community-associated isolates had both MIC_{50} and MIC_{90} of 0.5 mg/L.
- Compared to community-associated MRSA clones plus hospital-associated CC22 (MIC_{50} and MIC_{90}, of 0.5 and 0.5 mg/L respectively), CC8 had a slightly raised MIC_{50} and MIC_{90} (1 and 2 mg/L respectively).

References

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