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Ceftaroline Activity Tested Against Uncommonly Isolated Gram-positive Pathogens (2008- 2011)

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Amended Abstract

Objective: To evaluate ceftaroline (CPT) activity against uncommon gram-positive (GP) organisms. Very limited data is generally available on the antimicrobial susceptibility (S) of rarely occurring GP organisms. CPT, the active metabolite of CPT fosamil, a new cephalosporin approved by the European Medicines Agency and USA-FDA for similar indications, has shown in vitro activity against GP pathogens, including many multidrug-resistant isolates, and common gram-negative pathogens.

Methods: 1,859 clinically-significant GP isolates (31 species/groups) were collected over a 4-year period (SENTRY Programme, 2008-2011). The collection includes 1,273 streptococci (β-haemolytic [BHS] and viridans group [VGS]), 512 coagulase-negative staphylococci (CoNS), and 74 isolates from other GP species. The majority of isolates were from 79 USA medical centres, whereas for 9 less common species isolates were obtained from worldwide centres (including 54 non-USA centres). Isolates were submitted to a reference monitoring laboratory where species identifications were confirmed using MALDI-TOF when necessary. MIC testing and S determination for CPT and comparators used reference CLSI methods and quality assurance criteria.

Results: Isolates were primarily recovered from bacteremias (55%) and skin and soft tissue infections (20%). CPT was highly active against all BHS and VGS species/groups listed with MIC_{50} and MIC_{90} values ranging from ≤0.015 to 0.03 mg/L and ≤0.015 to 0.5 mg/L, respectively (Table 2). When tested against streptococci, the most CPT-S organisms were serogroup G, *S. bovis* group, *S. dysgalactiae* and *S. gordonii* (MIC_{90}, ≤0.015 mg/L), whereas the highest CPT MIC values were observed among *S. oralis* and *S. mitis*. CoNS species were generally very CPT-S, with MIC_{50} of 0.06 to 0.5 mg/L, regardless of methicillin S. Higher CPT MICs were observed among *S. haemolyticus* ($MIC_{50/90}$, 0.5/2 mg/L) compared to other CoNS species. CPT was generally two- to 16-fold more potent than vancomycin ($MIC_{50/90}$, 1/1-2 mg/L) when tested against CoNS. CPT was very active against *Micrococcus* spp., but showed more limited activity versus some *Corynebacterium* spp. and *L. monocytogenes* isolates.

Conclusions: CPT exhibited potent in vitro activity against many uncommonly isolated GP pathogens for which very limited S information is currently available to guide therapy. CPT may have a potential role in the treatment of infections caused by these species as guided by reference MIC test results.

Introduction

Ceftaroline fosamil, the prodrug form of ceftaroline, is a parenteral cephalosporin that was approved by the United States Food and Drug Administration (USA-FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), and more recently by the European Medicines Agency (EMA) for the treatment of complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP). Ceftaroline has demonstrated bactericidal activity in vitro against resistant gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) *Streptococcus pneumoniae*, as well as common gram-negative organisms.

Regulatory agencies and the Clinical and Laboratory Standards Institute (CLSI) have established ceftaroline breakpoint interpretive criteria for indicated staphylococcal and streptococcal species. These criteria are very helpful for clinical laboratories in guiding therapy for serious gram-positive infections; however, numerous other non-indicated gram-positive pathogens could require ceftaroline as a treatment option due to resistance or intolerance of other agents. To address this therapeutic possibility, we expand the knowledge of ceftaroline in vitro activity and spectrum by studying the compound against 31 gram-positive species/groups that are uncommonly isolated from contemporary clinical infections.

Methods

A total of 1,859 clinically significant gram-positive isolates were collected over a 4-year period (2008-2011). The collection includes 1,273 streptococci (β-haemolytic [BHS] and viridans group [VGS]), 512 coagulase-negative staphylococci (CoNS), and 74 isolates from other gram-positive species. The organisms were obtained from the SENTRY Antimicrobial Surveillance Programme from infections cultured in 133 medical centres located worldwide. The majority of isolates were from 79 USA medical centres, whereas for nine less common species, isolates were obtained from worldwide hospital locations. Isolates were primarily recovered from bacteremias (55%) and skin and soft tissue infections (20%). Isolates were submitted to a reference monitoring laboratory where species identifications were confirmed using MALDI-TOF, when necessary.

Minimum inhibitory concentration (MIC) testing and susceptibility determination for ceftaroline and comparators used reference CLSI methods and quality control criteria. The cation-adjusted Mueller-Hinton broth was supplemented with 2.5-5% lysed horse blood when testing fastidious streptococcal species. All quality control results were within published ranges for ceftaroline when testing *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619.

Results

- CoNS species were generally very susceptible to ceftaroline with a MIC_{50} of 0.06 to 0.5 mg/L. The lowest ceftaroline MIC values were observed with *Staphylococcus capitis* ($MIC_{50/90}$, 0.06/0.5 mg/L), whereas somewhat higher ceftaroline MIC values were observed among *S. haemolyticus* ($MIC_{50/90}$, 0.5/2 mg/L) compared to other CoNS species (Table 1)
- The MIC_{90} values for all staphylococcal species other than *S. haemolyticus* were ≤1 mg/L, and the highest MIC value observed for any CoNS species was 2 mg/L
- The highest oxacillin susceptibility rate was observed for the *S. lugdunensis* (95.4%), since this is the only CoNS species for which a higher susceptible breakpoint of ≤2 mg/L should be applied. Oxacillin susceptibility (MIC, ≤0.25 mg/L) was also relatively high for *S. capitis* (75.4%); while the lowest oxacillin susceptibility rates were observed among *S. sciuri* (5.7%), *S. cohnii* (6.7%) and *S. saprophyticus* (7.7%). Among *S. haemolyticus*, 31.8% of strains were susceptible to oxacillin (data not shown)
- Ceftaroline was very active against *Micrococcus* spp. ($MIC_{50/90}$, 0.06/0.06 mg/L), but showed more limited activity versus some *Corynebacterium* spp. isolates ($MIC_{50/90}$, 0.5/>32 mg/L) and *L. monocytogenes* isolates ($MIC_{50/90}$, 4/4 mg/L; Table 1)
- Ceftaroline was highly active against all BHS (non-serogroups A and B) and VGS species/groups tested with MIC_{50} and MIC_{90} values ranging from ≤0.015 to 0.03 mg/L and ≤0.015 to 0.5 mg/L, respectively (Table 2)
- When tested against streptococci, the most ceftaroline-susceptible organisms were serogroup G, *S. bovis* group, *S. dysgalactiae* and *S. gordonii* (MIC_{90}, ≤0.015 mg/L). In contrast, the highest ceftaroline MIC values were observed among *S. oralis* ($MIC_{50/90}$, 0.03/0.5 mg/L) and *S. mitis* ($MIC_{50/90}$, 0.03/0.25 mg/L; Table 2)
- The streptococcal species/groups less susceptible to penicillin were *S. parasanguinis* (MIC_{90}, 4 mg/L; 34.3% susceptible), *S. salivarius/S. vestibularis* (MIC_{90}, 0.5 mg/L; 42.9% susceptible), *S. sanguinis* (MIC_{90}, 1 mg/L; 62.9% susceptible), *S. mitis* (MIC_{90}, 2 mg/L; 65.5% susceptible), and *S. oralis* (MIC_{90}, 1 mg/L; 72.0% susceptible; data not shown).

Table 1. Uncommonly isolated staphylococcal species and other gram-positive pathogens (586 strains) tested by reference CLSI methods against ceftaroline

	No. (cumulative % inhibited) at ceftaroline MIC in mg/L									MIC (mg/L)	
Organism (no. tested)	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	≥4	50%	90%
Coagulase-negative staphylococci (512)											
S. auricularis (17)	-	1 (5.9)	5 (35.3)	6 (70.6)	4 (94.1)	0 (94.1)	1 (100.0)	-	-	0.12	0.25
S. capitis (65)	4 (6.2)	11 (23.1)	31 (70.8)	6 (80.0)	4 (86.2)	9 (100.0)	-	-	-	0.06	0.5
S. cohnii (15)	-	-	1 (6.7)	7 (53.3)	5 (86.7)	2 (100.0)	-	-	-	0.12	0.5
S. haemolyticus (66)	-	-	1 (1.5)	9 (15.2)	13 (43.9)	19 (63.6)	10 (78.8)	14 (100.0)	-	0.5	2
S. hominis (119)	-	2 (1.7)	6 (6.7)	22 (25.2)	31 (51.3)	40 (84.9)	18 (100.0)	-	-	0.25	1
S. lugdunensis (87)	-	-	1 (1.2)	21 (25.3)	57 (90.8)	8 (100.0)	-	-	-	0.25	0.25
S. saprophyticus (26)	-	-	2 (7.7)	2 (15.4)	16 (76.9)	6 (100.0)	-	-	-	0.25	0.5
S. sciuri (18)	-	-	0 (0.0)	3 (16.7)	9 (66.7)	2 (77.8)	3 (94.4)	1 (100.0)	-	0.25	1
S. simulans (24)	-	1 (4.2)	4 (20.8)	11 (66.7)	6 (91.7)	2 (100.0)	-	-	-	0.12	0.25
S. warneri (38)	-	1 (2.6)	10 (29.0)	12 (60.5)	5 (73.7)	9 (97.4)	1 (100.0)	-	-	0.12	0.5
S. xylosus (37)	-	3 (8.0)	3 (16.2)	4 (27.0)	21 (83.8)	6 (100.0)	-	-	-	0.25	0.5
Other species (74)											
Corynebacterium spp. (19)[a]	1 (5.3)	1 (10.5)	2 (21.1)	2 (31.6)	3 (47.4)	5 (73.7)	0 (73.7)	1 (79.0)	4 (100.0)	0.5	>32
Listeria monocytogenes (39)	-	-	-	-	-	-	1 (2.6)	4 (12.8)	34 (100.0)	4	4
Micrococcus spp. (16)	1 (6.3)	2 (18.8)	12 (93.8)	1 (100.0)	-	-	-	-	-	0.06	0.06

a. Includes *Corynebacterium amycolatum* (6), *C. aurimucosum* (1), *C. jeikeium* (3), *C. pseudodiptheriticum* (1), and *C. striatum* (8).

Table 2. Uncommon streptococcal species (1,273 strains) tested against ceftaroline, a newer anti-MRSA cephalosporin

	No. (cumulative % inhibited) at ceftaroline MIC in mg/L							MIC (mg/L)	
Group/organism (no. tested)	≤0.015	0.03	0.06	0.12	0.25	0.5	1	50%	90%
Serogroup C (207)	154 (74.4)	49 (98.1)	4 (100.0)	-	-	-	-	≤0.015	0.03
Serogroup F (56)	17 (30.4)	30 (83.9)	9 (100.0)	-	-	-	-	0.03	0.06
Serogroup G (335)	328 (97.9)	6 (99.7)	1 (100.0)	-	-	-	-	≤0.015	≤0.015
S. anginosus group									
S. anginosus (124)	49 (39.5)	68 (94.4)	7 (100.0)	-	-	-	-	0.03	0.03
S. constellatus (44)	13 (29.6)	20 (75.0)	10 (97.7)	0 (97.7)	1 (100.0)	-	-	0.03	0.06
S. intermedius (22)	19 (86.4)	2 (95.5)	1 (100.0)	-	-	-	-	≤0.015	0.03
S. bovis group (47)[a]	47 (100.0)	-	-	-	-	-	-	≤0.015	≤0.015
S. dysgalactiae group									
S. dysgalactiae (32)	32 (100.0)	-	-	-	-	-	-	≤0.015	≤0.015
S. equisimilis (18)	16 (88.9)	2 (100.0)	-	-	-	-	-	≤0.015	0.03
S. mitis group									
S. mitis (197)	89 (45.2)	50 (70.6)	26 (83.8)	12 (89.9)	2 (90.9)	9 (95.4)	9 (100.0)	0.03	0.25
S. gordonii (13)	12 (92.3)	1 (100.0)	-	-	-	-	-	≤0.015	≤0.015
S. oralis (25)	7 (28.0)	11 (72.0)	2 (80.0)	0 (80.0)	2 (88.0)	2 (96.0)	1 (100.0)	0.03	0.5
S. parasanguinis (35)	17 (48.6)	6 (65.7)	6 (82.9)	3 (91.4)	0 (91.4)	0 (91.4)	3 (100.0)	0.03	0.12
S. sanguinis (35)	24 (68.6)	6 (85.7)	2 (91.4)	2 (97.1)	1 (100.0)	-	-	≤0.015	0.06
S. mutans group									
S. mutans (20)	16 (80.0)	0 (80.0)	2 (90.0)	2 (100.0)	-	-	-	≤0.015	0.06
S. salivarius/S. vestibularis group (49)	27 (55.1)	16 (87.8)	5 (98.0)	1 (100.0)	-	-	-	≤0.015	0.06
S. milleri group (14)[b]	6 (42.9)	8 (100.0)	-	-	-	-	-	0.03	0.03

a. Includes: *S. bovis* group NOS (31), *S. gallolyticus* (13), and *S. infantarius* (3).
b. Taxonomy unclear but most closely related to *S. anginosus* group.

Conclusions

- Ceftaroline exhibited potent in vitro activity against many rare gram-positive pathogens for which susceptibility information is currently less available to guide therapy
- Ceftaroline may have a potential role in the treatment of infections caused by these species as guided by reference MIC test results or published literature.

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