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Antimicrobial activity of ceftaroline and comparator agents when tested against numerous species of coagulase-negative *Staphylococcus* causing infection in US hospitals

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ABSTRACT

A total of 1593 coagulase-negative staphylococci (CoNS) considered clinically significant were collected from 71 US medical centers in 2013–2014 and tested for susceptibility by CLSI broth microdilution methods. Species identification was performed by matrix-assisted laser desorption ionization–time-of-flight mass spectrometry. Overall, 59.7% of isolates were oxacillin resistant (MRCoNS). Ceftaroline ($MIC_{50/90}$, 0.25/0.5 μg/mL) inhibited 99.2% of CoNS at ≤1 μg/mL (susceptible breakpoint for *Staphylococcus aureus*), including 98.7% of MRCoNS, and the highest ceftaroline MIC value was 2 μg/mL (13 isolates). *Staphylococcus epidermidis* represented 60.3% of the CoNS collection and was highly susceptible to ceftaroline ($MIC_{50/90}$, 0.25/0.5 μg/mL, 99.9% inhibited at ≤1 μg/mL). All isolates of *Staphylococcus capitis*, *Staphylococcus caprae*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Staphylococcus pettenkoferi*, *Staphylococcus simulans*, and *Staphylococcus warneri* ($MIC_{50/90}$, 0.06–0.25/0.25–0.5 μg/mL) were inhibited at ceftaroline MIC of ≤1 μg/mL. *Staphylococcus haemolyticus* represented only 4.8%, was atypically less susceptible to ceftaroline ($MIC_{50/90}$, 0.5/2 μg/mL, 87.0% inhibited at ≤1 μg/mL), and accounted for 76.9% (10/13) of isolates with ceftaroline MIC >1 μg/mL.

1. Introduction

Changes in the patient population, including increasing number of elderly, premature newborn, and chronically ill and immunocompromised patients, led to the recognition of a large variety of infections caused by coagulase-negative staphylococci (CoNS) (Argemi et al., 2015; Becker et al., 2014). Moreover, the widespread use of matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF-MS) has allowed a better understanding of the clinical importance of different CoNS species (Argemi et al., 2015; Becker et al., 2014). CoNS represent the most common cause of bacteremia related to indwelling devices, and most of these infections are hospital acquired (Sievert et al., 2013). Other important infections caused by CoNS include orthopedic device- and various implant-associated infections, central nervous system shunt infections, native or prosthetic valve endocarditis, urinary tract infections (UTIs), skin and skin structure infections (SSSIs), surgical site infections, and endophthalmitis (Becker et al., 2014; Bocher et al., 2009; Sievert et al., 2013).

Resistance to oxacillin and other β-lactams is widespread among CoNS associated with human infections, and the basic mechanisms leading to a reduced susceptibility to glycopeptides, such as cell wall thickening, appear to be similar in CoNS and *Staphylococcus aureus*. Thus, although CoNS are usually susceptible to glycopeptides, increased MIC values for teicoplanin (≥4 μg/mL) and/or vancomycin (≥2 μg/mL) are frequently reported and may relate to poor clinical treatment outcomes (Becker et al., 2014; Biavasco et al., 2000; Cremniter et al., 2010; Tacconelli et al., 2001).

Ceftaroline fosamil, the prodrug of ceftaroline, is a broad-spectrum parenteral cephalosporin which was approved by the US Food and Drug Administration (USA-FDA) for the treatment of acute bacterial SSSI (ABSSSI) and community-acquired bacterial pneumonia and by the European Medicines Agency for the treatment of complicated skin and soft tissue infections and community-acquired pneumonia (TEFLARO®, 2015; Zinforo®, 2015). Ceftaroline has demonstrated potent in vitro bactericidal activity against resistant Gram-positive organisms, including methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae*, as well as prevalent Gram-negative organisms (Critchley et al., 2011; Sader et al., 2015). In the present investigation, we evaluated the in vitro activity of ceftaroline and many comparator agents tested against a large collection of CoNS from US hospitals.

2. Materials and methods

2.1. Organism collection

A total of 1593 CoNS isolates considered clinically significant (multiple infection types) were collected from 71 US medical centers in

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2013–2014 (1/patient episode) through the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance program (Sader et al., 2015). All medical centers collected the strains following a common protocol, and only isolates determined to be significant by local criteria as the reported probable cause of the infection were included in this surveillance program. Culture of clinical specimens and species identification were performed at the participant medical centers according to local guidelines. The AWARE program monitors many bacteria genus/species from various infection types, and all CoNS isolates submitted to the program in 2013 and 2014 were included in this investigation. Isolates were submitted to a reference monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) where species identifications were confirmed by MALDI-TOF-MS using the Biotyper system according to manufacturer recommendations (Bruker Daltonics, Bremen, Germany).

2.2. Antimicrobial susceptibility testing

All isolates were tested for susceptibility at the monitoring laboratory (JMI Laboratories) by broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI, 2015a). Susceptibility testing was performed using validated broth microdilution panels (Sensititre®) manufactured by Thermo Fisher Scientific (Cleveland, OH, USA). Categorical interpretation of MIC values was performed according to CLSI (2015b) and EUCAST (2015), i.e., an oxacillin susceptible breakpoint of ≤0.25 μg/mL was applied for all species except for *Staphylococcus lugdunensis*, for which a susceptible breakpoint of ≤2 μg/mL was applied. Percentage of strains inhibited at ceftaroline MIC of ≤1 μg/mL, the susceptible breakpoint for *S. aureus*, is presented for comparison purpose since neither CLSI nor EUCAST has established ceftaroline breakpoints for CoNS. Validation of MIC values was performed by concurrent testing of CLSI-recommended quality control strains: *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.

3. Results

The most frequently isolated species overall were *Staphylococcus epidermidis* (960 isolates; 60.3%), *S. lugdunensis* (168 isolates; 10.5%), *Staphylococcus hominis* (120 isolates; 7.5%), and *Staphylococcus capitis* (103 isolates; 6.5%). Overall, 602 (37.8%) of isolates were from bloodstream infections (BSIs), 580 (36.4%) from SSSI, 164 (10.3%) from UTI, and 247 (15.5%) from other infection sites. Among isolates from BSI, the most common species were *S. epidermidis* (371; 61.6%), *S. hominis* (85; 14.1%), and *S. capitis* (103; 9.6%). Moreover, 82.1% of *S. lugdunensis* isolates were from SSSI, and 88.6% of *S. saprophyticus* isolates were from UTI.

Ceftaroline ($MIC_{50/90}$, 0.25/0.5 μg/mL) inhibited 99.2% of CoNS at ≤1 μg/mL (susceptible breakpoint for *S. aureus*), including 98.7% of oxacillin-resistant CoNS (Table 1). Among isolates from BSI, 99.3% (598/602) were inhibited at ceftaroline MIC of ≤1 μg/mL (Table 1), and isolates with ceftaroline MIC >1 μg/mL were 3 *Staphylococcus haemolyticus* and 1 *Staphylococcus cohnii* isolates with ceftaroline MIC of 2 μg/mL.

Overall, 59.7% of isolates were oxacillin resistant (MRCoNS). Oxacillin resistance rates varied from as low as 1.8% for *S. lugdunensis* and 27.2% for *S. capitis* to as high as 76.3% for *Staphylococcus warneri* and 100.0% for *Staphylococcus saprophyticus* (Table 2). Among *S. epidermidis*, oxacillin resistance rate was slightly higher for BSI isolates (76.0%), compared to non-BSI isolates (68.4%).

Susceptibility rates were generally low for erythromycin (36.9%; varying from 20.8% to 79.2%), clindamycin (68.9%; varying from 59.0% to 88.6%), levofloxacin (58.3%, varying from 41.6% to 100.0%), tetracycline (85.1%; varying from 61.0% to 94.3%), and trimethoprim-sulfamethoxazole (TMP-SMX) (70.5%, varying from 60.0% to 99.4%), with great variability among species (Table 2). Lowest susceptibility rates were observed for *S. epidermidis*, *S. haemolyticus*, and *S. hominis*, whereas the highest susceptibility rates for these antimicrobial agents were observed among *S. lugdunensis*, *S. saprophyticus*, and *S. warneri* (Table 2).

Vancomycin (100.0% susceptibility), daptomycin (99.9%), linezolid (99.3%), and tigecycline (100.0% susceptibility by EUCAST criteria) were very active against all CoNS species, and teicoplanin susceptibility (CLSI/EUCAST) varied from 90.9/76.6% for *S. haemolyticus* to 100.0/>99.0% for *S. lugdunensis* and *S. saprophyticus* (Table 2).

Susceptibility to daptomycin was 99.9%, with only 2 daptomycin-nonsusceptible strains (both with daptomycin MIC of 2 μg/mL) being observed, 1 *S. capitis* and 1 *Staphylococcus pettenkoferi*. Linezolid was active against, 99.3% of isolates (MIC_{50} and MIC_{90}, 0.5 μg/mL; Table 2); all linezolid-nonsusceptible isolates (n = 11; 0.7%) were *S. epidermidis*, and 7 of them (63.6%) were from BSI.

Ceftaroline activity ($MIC_{50/90}$, 0.25–0.5 μg/mL; 99.2% inhibited at ≤1 μg/mL) was 4-fold greater than that of vancomycin ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible) and similar to that of daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL; 99.9% susceptible; Table 2). Tigecycline ($MIC_{50/90}$, 0.06–0.12 μg/mL; 100.0% susceptible at ≤0.5 μg/mL [EUCAST]) was the most potent (lower MIC_{50} and MIC_{90} values) compound tested (Table 2).

The highest ceftaroline MIC value was only 2 μg/mL, which was observed only among *S. cohnii* (1 of 7; 14.3%), *S. epidermidis* (0.1%), *S. haemolyticus* (13.0%), and *S. saprophyticus* (2.9%; Tables 1 and 2). *S. epidermidis* was highly susceptible to ceftaroline ($MIC_{50/90}$, 0.25/0.5 μg/mL, 99.9% inhibited at ≤1 μg/mL). *S. lugdunensis* and *S. hominis* ($MIC_{50/90}$, 0.25/0.5 μg/mL for both) were the second and third most common CoNS species, respectively, and *S. capitis* ($MIC_{50/90}$, 0.06/0.25 μg/mL) ranked 4th; all isolates from these 3 species were inhibited at ceftaroline MIC of ≤1 μg/mL (Tables 1 and 2). Moreover, all isolates of *Staphylococcus caprae* ($MIC_{50/90}$, 0.06/0.12 μg/mL; highest MIC,

Table 1
Summary of ceftaroline activity tested against 1593 clinical isolates of coagulase-negative staphylococci from US medical centers (2013–2014).

Organism/no. tested	No. of isolates (cumulative %) inhibited at MIC (μg/mL) of							MIC (μg/mL)	
	≤0.03	0.06	0.12	0.25	0.5	1	2	50%	90%
S. capitis (103)	36 (35.0)	43 (76.7)	5 (81.6)	10 (91.3)	6 (97.1)	3 (100.0)		0.06	0.25
S. caprae (13)	1 (7.7)	8 (69.2)	3 (92.3)	0 (92.3)	1 (100.0)			0.06	0.12
S. epidermidis (960)	28 (2.9)	181 (21.8)	124 (34.7)	354 (71.6)	257 (98.3)	15 (99.9)	1 (100.0)	0.25	0.5
S. haemolyticus (77)		1 (1.3)	14 (19.5)	18 (42.9)	21 (70.1)	13 (87.0)	10 (100.0)	0.5	2
S. hominis (120)		6 (5.0)	37 (35.8)	26 (57.5)	43 (93.3)	8 (100.0)		0.25	0.5
S. lugdunensis (168)		4 (2.4)	24 (16.7)	121 (88.7)	17 (98.8)	2 (100.0)		0.25	0.5
S. pettenkoferi (10)		1 (10.0)	6 (70.0)	3 (100.0)				0.12	0.25
S. saprophyticus (35)			7 (20.0)	18 (71.4)	6 (88.6)	3 (97.1)	1 (100.0)	0.25	1
S. simulans (27)		8 (29.6)	12 (74.1)	7 (100.0)				0.12	0.25
S. warneri (38)	1 (2.6)	10 (28.9)	19 (78.9)	2 (84.2)	5 (97.4)	1 (100.0)		0.12	0.5
Other species (42)[a]	1 (2.4)	3 (9.5)	17 (50.0)	11 (76.2)	4 (85.7)	5 (97.6)	1 (100.0)	0.12	1
All isolates (1593)	67 (4.2)	265 (20.8)	268 (37.7)	570 (73.4)	360 (96.0)	50 (99.2)	13 (100.0)	0.25	0.5
Isolates from BSI (602)	27 (4.7)	90 (19.7)	104 (37.0)	185 (67.7)	165 (95.1)	26 (99.3)	4 (100.0)	0.25	0.5

[a] Organisms include *Staphylococcus arlettae* (1), *Staphylococcus auricularis* (5), *Staphylococcus schleiferi* (4), *S. cohnii* (7), *Staphylococcus intermedius* (4), *Staphylococcus lentus* (3), *Staphylococcus pasteuri* (2), *Staphylococcus pseudintermedius* (6), *S. pseudintermedius/intermedius* (5), *Staphylococcus sciuri* (2), unspeciated *Staphylococcus* (2), and *Staphylococcus xylosus* (1).