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Antimicrobial activity of ceftaroline combined with avibactam tested against bacterial organisms isolated from acute bacterial skin and skin structure infections in United States medical centers (2010–2012)

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ABSTRACT

Ceftaroline-avibactam and comparator agents were tested against clinical isolates collected at 174 medical centers from patients with acute bacterial skin and skin structure infection (ABSSSI) in the United States (USA) during 2010–2012. Isolates were processed at the medical centers and forwarded to a central laboratory for confirmatory identification and susceptibility testing using reference methods. Ceftaroline-avibactam was highly active against methicillin-susceptible ($MIC_{50/90}$, 0.25/0.25 μg/mL) and methicillin-resistant *Staphylococcus aureus* (MRSA; $MIC_{50/90}$, 0.5/1 μg/mL). Vancomycin, tigecycline, daptomycin, and linezolid were also active (>99.9% susceptible) against MRSA (51.4% of *S. aureus*), but activity against MRSA was decreased for erythromycin, levofloxacin, and clindamycin (10.8, 40.3, and 81.9% susceptible, respectively). β-Hemolytic streptococci were highly susceptible to β-lactam antimicrobials, including ceftaroline-avibactam ($MIC_{50/90}$, ≤0.03/≤0.03 μg/mL). Ceftaroline-avibactam was very active against *Escherichia coli* and *Klebsiella pneumoniae* ($MIC_{50/90}$, 0.03/0.06 and 0.06/0.25 μg/mL, respectively) including extended-spectrum β-lactamase (ESBL) screen–positive phenotypes ($MIC_{50/90}$, 0.06/0.12 and 0.12/1 μg/mL, respectively). Susceptibility of ESBL screen–positive *E. coli* and *K. pneumoniae* was 100.0/97.9% for tigecycline and 99.2/56.1% for meropenem, respectively. Susceptibility to other agents for ESBL screen–positive *E. coli* and *K. pneumoniae* was decreased. Ceftaroline-avibactam exhibited a broad-spectrum of in vitro activity against isolates from patients in the USA with ABSSSI including MRSA, β-hemolytic streptococci, *E. coli*, and *K. pneumoniae* as well as ESBL screen–positive phenotype isolates and merits further study in clinical indications where these resistant organisms may be a concern.

1. Introduction

Acute bacterial skin and skin structure infections (ABSSSI) are common infections representing approximately 10% of hospital admissions (Dryden, 2010; Giordano et al., 2007; Stevens et al., 2005). ABSSSI can range from mild infections to serious and even life-threatening infections (Dryden, 2010; Stevens et al., 2005). The most common bacterial causes of ABSSSI include *Staphylococcus aureus* and β-hemolytic streptococci (Dryden, 2010; Moet et al., 2007; Sader et al., 2013a; Stevens et al., 2005). In hospitals, *S. aureus* predominates as the major cause of ABSSSI (Dryden, 2010). Gram-negative bacteria, primarily Enterobacteriaceae and non-fermentative bacteria such as *Pseudomonas aeruginosa* may also cause ABSSSI (Dryden, 2010; Moet et al., 2007; Stevens et al., 2005). The emergence of resistance to multiple classes of antimicrobials in methicillin-resistant *S. aureus* and Gram-negative bacilli, especially in immunocompromised patients, has added complexity to choosing appropriate initial therapy (Dryden, 2010; Moet et al., 2007).

Ceftaroline-avibactam is a combination of the antibacterial ceftaroline and the novel non-β-lactam β-lactamase inhibitor avibactam (Castanheira et al., 2012; Goldstein et al., 2013; Livermore et al., 2012; Mushtaq et al., 2010; Sader et al., 2013b; Wiskirchen et al., 2011). Avibactam does not have intrinsic antibacterial activity; however, it does inhibit Class A and C and some Class D β-lactamases (Ehmann et al., 2012). When avibactam is combined with an active β-lactam agent, such as ceftaroline, its ability to inhibit β-lactamases protects the activity of the β-lactam from β-lactamase degradation (Castanheira et al., 2012; Goldstein et al., 2013; Livermore et al., 2012; Mushtaq et al., 2010; Sader et al., 2013b; Wiskirchen et al., 2011). Ceftaroline fosamil, the prodrug of active ceftaroline, is a cephalosporin approved by the United States Food and Drug Administration (USA-FDA) and European Medicines Agency. Ceftaroline has broad-spectrum bactericidal in vitro activity against resistant Gram-positive organisms, including methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant (MDR) strains of *Streptococcus pneumoniae* (Flamm et al., 2012; Sader et al., 2013a; Saravolatz et al., 2011; Teflaro® Package Insert, 2012; Zinforo™ Package Insert, 2012).

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Ceftaroline also has activity against many Enterobacteriaceae; however, it is not active against extended-spectrum β-lactamase (ESBL) phenotype strains (Flamm et al., 2012; Sader et al., 2013a; Saravolatz et al., 2011). Adding avibactam to ceftaroline expands the activity to include ESBL and cephalosporinase phenotype strains (Castanheira et al., 2012; Flamm et al., 2012; Livermore et al., 2012; Mushtaq et al., 2010; Sader et al., 2013a; Wiskirchen et al., 2011).

In an effort to better understand the activity of ceftaroline-avibactam when tested against ABSSSI pathogens in the USA and to provide information on the baseline level of activity for this agent, a surveillance program to assess ceftaroline-avibactam and comparator agents was performed. Herein, we report the results for a 3-year period (2010–2012) describing the activities against 14,504 isolates from documented ABSSSI collected from patients in 174 different medical centers.

2. Materials and methods

2.1. Organism collection

Organisms were collected from patients with ABSSSI (1 per patient episode). A total of 14,504 were tested against ceftaroline-avibactam as listed in Table 1. The study protocol predetermined the target numbers of strains for each of the requested bacterial species that sites were to collect. One hundred seventy-four different medical centers representing all 9 USA census bureau regions submitted isolates during the time period 2010–2012; 65 medical centers (5–10 medical centers per region, 37 states in 2010), 67 medical centers (5–12 medical centers per region, 37 states in 2011), and 163 medical centers (7–27 medical centers per region, 47 states in 2012). Isolates were sent to a central reference laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmatory identification and reference susceptibility testing.

2.2. Susceptibility testing

Susceptibility testing was performed for ceftaroline-avibactam and selected comparator agents by reference broth microdilution methods as described by the CLSI document M07-A9 (CLSI, 2012). Avibactam was tested at a fixed concentration of 4 μg/mL. CLSI interpretive criteria were applied per M100-S23 (CLSI, 2013) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretations were based on EUCAST breakpoint table v.3.0, January 2013 (EUCAST, 2013). USA-FDA breakpoint criteria for tigecycline were applied, when available (Tygacil® Package Insert, 2012).

The susceptibility test medium used was cation-adjusted Mueller-Hinton broth; however, for β-hemolytic streptococci, supplementation with 2.5–5% lysed horse blood was done (CLSI, 2012). Quality control (QC) strains were tested concurrently and included *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, and *Escherichia coli* ATCC 25922 and 35218. All QC results were within published CLSI ranges (CLSI, 2013). *E. coli* and *Klebsiella* spp. isolates were identified as phenotypically positive by a screening test for ESBL production when ceftriaxone or ceftazidime or aztreonam MIC values were ≥2 μg/mL (CLSI, 2013). Although an ESBL confirmation test was not performed and other β-lactamases, such as AmpC and *K. pneumoniae* carbapenemases (KPC), may also produce an "ESBL-phenotype", these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds. As part of a specific program to examine the diversity of β-lactamases found in Gram-negative bacteria in the USA during 2012, Gram-negative bacteria that occurred in skin and skin structure infections collected during 2012 that were positive by the screening method for ESBL phenotype were evaluated further for the presence of broad-spectrum β-lactamases as previously described using a commercial microarray-based assay Check-MDR CT101 kit (Check-points, Wageningen, Netherlands) (Castanheira et al., 2013; Castanheira et al., 2014). This kit has the capability to detect CTX-M

Table 1
Summary of ceftaroline-avibactam activity tested against bacterial isolates from patients with acute bacterial skin and skin structure infections from the USA (2010–2012).

Organism	No. of isolates	No. of isolates (cumulative %) inhibited at ceftaroline-avibactam MIC (μg/mL):									
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	MIC_{50}	MIC_{90}
S. aureus	8422	5 (0.1)	35 (0.5)	622 (7.9)	3438 (48.7)	3431 (89.4)	843 (99.4)	48 (100.0)	–	0.5	1
MSSA	4089	5 (0.1)	35 (1.0)	620 (16.1)	3328 (97.5)	101 (100.0)	–	–	–	0.25	0.25
MRSA	4333	–	–	2 (0.0)	110 (2.6)	3330 (79.4)	843 (98.9)	48 (100.0)	–	0.5	1
CoNS	622	52 (8.4)	133 (29.7)	101 (46.0)	252 (86.5)	77 (98.9)	6 (99.8)	1 (100.0)		0.25	0.5
β-hemolytic streptococci	1523	1,512 (99.3)	11 (100.0)	–	–	–	–	–	–	≤0.03	≤0.03
Streptococcus pyogenes	706	706 (100.0)	–	–	–	–	–	–	–	≤0.03	≤0.03
Streptococcus agalactiae	671	669 (99.7)	2 (100.0)	–	–	–	–	–	–	≤0.03	≤0.03
Other streptococci	146	137 (93.8)	9 (100.0)							≤0.03	≤0.03
Viridans group streptococci	411	353 (85.9)	37 (94.9)	6 (96.4)	6 (97.8)	6 (99.3)	3 (100.0)	–	–	≤0.03	0.06
E. coli	923	687 (74.4)	201 (96.2)	28 (99.2)	3 (99.6)	4 (100.0)	–	–	–	≤0.03	0.06
ESBL screen–negative phenotype	805	635 (78.9)	160 (98.8)	10 (100.0)	–	–	–	–	–	≤0.03	0.06
ESBL screen–positive phenotype	118	52 (44.1)	41 (78.8)	18 (94.1)	3 (96.6)	4 (100.0)	–	–	–	0.06	0.12
Meropenem-susceptible (MIC, ≤1 μg/mL)	922	687 (74.5)	200 (96.2)	28 (99.2)	3 (99.6)	4 (100.0)	–	–	–	≤ 0.03	0.06
Meropenem-non-susceptible (MIC, ≥2 μg/mL)	1	–	1 (100.0)	–	–	–	–	–	–	–	–
K. pneumoniae	641	146 (22.8)	319 (72.5)	94 (87.2)	46 (94.4)	26 (98.4)	6 (99.4)	2 (99.7)	2 (100.0)	0.06	0.25
ESBL screen–negative phenotype	543	139 (25.6)	305 (81.8)	65 (93.7)	26 (98.5)	8 (100.0)	–	–	–	0.06	0.12
ESBL screen–positive phenotype	98	7 (7.1)	14 (21.4)	29 (51.0)	20 (71.4)	18 (89.8)	6 (95.9)	2 (98.0)	2 (100.0)	0.12	1
Meropenem-susceptible (MIC, ≤1 mg/L)	598	145 (24.2)	319 (77.6)	86 (92.0)	35 (97.8)	13 (100.0)	–	–	–	0.06	0.12
Meropenem-non-susceptible (MIC, ≥2 μg/mL)	43	1 (2.3)	0 (2.3)	8 (20.9)	11 (46.5)	13 (76.7)	6 (90.7)	2 (95.3)	2 (100.0)	0.5	1
K. oxytoca	281	149 (53.0)	99 (88.3)	22 (96.1)	6 (98.2)	4 (99.6)	1 (100.0)	–	–	≤0.03	0.12
Enterobacter spp.	599	65 (10.9)	172 (39.6)	237 (79.1)	79 (92.3)	36 (98.3)	10 (100.0)	–	–	0.12	0.25
Citrobacter spp.	208	59 (28.4)	107 (79.8)	33 (95.7)	7 (99.0)	1 (99.5)	1 (100.0)	–	–	0.06	0.12
P. mirabilis	413	49 (11.9)	244 (70.9)	102 (95.6)	14 (99.0)	2 (99.5)	2 (100.0)	–	–	0.06	0.12
M. morganii	239	137 (57.3)	66 (84.9)	21 (93.7)	11 (98.3)	3 (99.6)	1 (100.0)	–	–	≤0.03	0.12
S. marcescens	222	1 (0.5)	1 (0.9)	27 (13.1)	62 (41.0)	96 (84.2)	32 (98.6)	1 (99.1)	2 (100.0)	0.5	1

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