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In vitro activity of ceftaroline tested against isolates from the Asia-Pacific region and South Africa (2011)

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ABSTRACT

During 2011, 29 medical centres in eight Asia-Pacific countries and South Africa submitted a total of 3697 bacterial pathogens for surveillance testing, of which 39.1% were from respiratory tract, 27.9% from skin and skin-structure, 19.2% from bloodstream, 5.1% from urinary tract and 8.7% from miscellaneous infection types. Meticillin-resistant *Staphylococcus aureus* (MRSA) constituted 38.9% of the 1114 *S. aureus.* The MRSA rate was 53.5% for respiratory tract infections and 31.8% for skin and skin-structure infections. A total of 86.5% of *S. aureus* exhibited ceftaroline minimum inhibitory concentrations (MICs) at ≤1 μg/mL. Ceftaroline (MIC_{90}, 0.25 μg/mL) was eight-fold more active than ceftriaxone (MIC_{90}, 2 μg/mL) against *Streptococcus pneumoniae*; erythromycin and clindamycin susceptibility were severely compromised. Against β-haemolytic streptococci, ceftaroline and other β-lactams were highly active, with MIC_{90} values at 0.03 μg/mL. The extended-spectrum β-lactamase (ESBL) phenotype rate was 57.6% among *Escherichia coli*, 49.7% among *Klebsiella pneumoniae* and 23.7% among *Klebsiella oxytoca.* ESBL phenotype rates for *E. coli* ranged from a low of 8.3% in South Africa to a high of 77.9% in India. For *K. pneumoniae*, the ESBL phenotype rate ranged from 20.6% in Australia to 67.8% in India. Ceftaroline was active against non-ESBL-phenotype *E. coli* and *K. pneumoniae* (MIC_{90}, 0.25 μg/mL) but was not active against ESBL-phenotype strains (MIC_{90}, >32 μg/mL). Overall, ceftaroline demonstrated in vitro activity against pathogens isolated from various infection sites, including respiratory tract, bloodstream, and skin and skin-structure infections, across the monitored nations.

1. Introduction

Ceftaroline fosamil was approved for clinical use in the USA for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin-structure infections (ABSSSIs) in 2010, and for similar indications in Europe in 2012 [1,2]. Ceftaroline fosamil is a parenteral cephalosporin pro-drug that upon intravenous administration is metabolised to active ceftaroline, which has in vitro activity against meticillin-resistant *Staphylococcus aureus* (MRSA) owing to its affinity for penicillin-binding protein 2A (PBP2A) as well as against penicillin-resistant *Streptococcus pneumoniae* because of its affinity for PBP2x [3–6]. Clinical studies of ceftaroline fosamil have shown it to be non-inferior to ceftriaxone in patients with community-acquired pneumonia (NCT00621504 and NCT00509106) and non-inferior to vancomycin plus aztreonam in patients with ABSSSI (NCT00424190 and NCT00423657) [7–9].

The spectrum of activity of ceftaroline includes both Gram-positive and Gram-negative bacteria [2,3,7,10–17]. It is the only currently approved cephalosporin in the USA with activity against MRSA [1,2]. Furthermore, it has in vitro activity against multidrug-resistant *S. pneumoniae* as shown by Jones et al. and others [MIC_{50} and MIC_{90} values (minimum inhibitory concentrations required to inhibit 50% and 90% of the isolates, respectively), 0.12 μg/mL and 0.25 μg/mL] [3,10,12,13]. Ceftaroline also exhibits potent in vitro activity against *Haemophilus influenzae* (MIC_{90}, 0.008–0.015 μg/mL) and non-extended-spectrum β-lactamase (ESBL) phenotype Enterobacteriaceae [10–14,16]. This broad spectrum of activity makes ceftaroline fosamil an option for monotherapy of indicated infections (CABP and ABSSSI).

As a recently approved antibacterial agent, it is prudent to monitor the activity of ceftaroline through antimicrobial resistance surveillance in order to recognise potential emerging susceptibility trends. Surveillance studies of ceftaroline through the AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation)

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Programme on a global scale as well as others have been conducted [10–17]. These studies have indicated that ceftaroline exhibits in vitro activity against pathogens relevant to its approved indications, but there may be regional differences in levels of potency. For example, in the USA (2010) and Canada (2009), MIC_{90} values for MRSA were at 1 μg/mL, whilst in Europe (2010) the MIC_{90} value was 2 μg/mL [11,12,15]. In this report, we present the results for ceftaroline and comparator agents tested in a surveillance programme against pathogens isolated from patients in the Asia-Pacific region and South Africa during 2011.

2. Materials and methods

2.1. Isolate collection

A total of 3697 target bacterial pathogens were collected (one per patient infectious episode) from patients in participating medical centres in Australia (6 medical centres), China (10), Hong Kong (1), India (5), South Korea (2), Malaysia (1), Singapore (1), Thailand (2) and South Africa (1) during 2011. Isolates were sent to the co-ordinating laboratory (JMI Laboratories, North Liberty, IA; Australian isolates, South Australia Pathology, Women's & Children's Hospital, Adelaide, Australia) for confirmatory identification and reference susceptibility testing.

2.2. Susceptibility testing

Antimicrobial susceptibility testing was performed for ceftaroline and comparator agents according to Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methods [18]. CLSI or European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria were applied [19,20]; in the case of tigecycline, the US Food and Drug Administration (FDA) drug package insert interpretive criteria were used [21]. Media were cation-adjusted Mueller–Hinton broth, supplemented with 2.5–5% lysed horse blood for streptococci, and Haemophilus Test Medium for *Haemophilus* spp. [18]. Quality control (QC) testing was performed with the following QC strains: *S. aureus* ATCC 29213; *Enterococcus faecalis* ATCC 29212; *S. pneumoniae* ATCC 49619; *H. influenzae* ATCC 49247 and 49766; *Escherichia coli* ATCC 25922 and 35218; and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within published CLSI ranges [19]. Enterobacteriaceae that exhibited ceftriaxone, ceftazidime or aztreonam MICs of ≥2 μg/mL were defined as possessing an extended-spectrum β-lactamase (ESBL) phenotype [19].

3. Results

Of the 3697 target pathogens, 39.1% were from respiratory tract, 27.9% from skin and skin-structure, 19.2% from bloodstream, 5.1% from urinary tract and 8.7% from other infection types (data not shown). A total of 77.6% of all *S. aureus* were from respiratory tract infections and skin and skin-structure infections (SSSIs) (data not shown); 38.9% of all *S. aureus* were MRSA (Tables 1–3). MRSA represented 53.5% of *S. aureus* isolated from the respiratory tract, 39.7% from bloodstream infections, 31.8% from SSSIs and 47.0% from miscellaneous infections (data not shown).

A total of 86.5% of *S. aureus* exhibited ceftaroline MICs at ≤1 μg/mL (Tables 1 and 2), and 13.4% of isolates (all of which were MRSA) exhibited MICs of 2 μg/mL (Tables 1 and 2). *Staphylococcus aureus* (MRSA) with MICs at 2 μg/mL occurred in all countries (data not shown). There was one MRSA isolate from Thailand with a ceftaroline MIC of 4 μg/mL (Tables 1 and 2). All *S. aureus* isolates were susceptible to linezolid, teicoplanin and tigecycline and all but one isolate were susceptible to vancomycin (Table 2). The one vancomycin-intermediate isolate was an MRSA isolate from a

Table 1
Summary of ceftaroline activity tested against pathogen groups from Asia-Pacific and South Africa (2011).

Organism (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline MIC (μg/mL) of												MIC (μg/mL)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Staphylococcus aureus (1114)	–	–	1 (0.1)	63 (5.7)	605 (60.1)	185 (76.7)	110 (86.5)	149 (99.9)	1 (100.0)	–	–	–	–	0.25	2
MSSA (681)	–	–	1 (0.1)	62 (9.3)	602 (97.7)	16 (100.0)	–	–	–	–	–	–	–	0.25	0.25
MRSA (433)	–	–	–	1 (0.2)	3 (0.9)	169 (40.0)	110 (65.4)	149 (99.8)	1 (100.0)	–	–	–	–	1	2
Streptococcus pneumoniae (636)	329 (51.7)	31 (56.6)	39 (62.7)	140 (84.7)	63 (94.7)	32 (99.7)	2 (100.0)	–	–	–	–	–	–	≤0.015	0.25
S. pneumoniae, Pen^R (MIC ≥ 8 μg/mL) (22)	–	–	–	–	11 (50.0)	10 (95.5)	1 (100.0)	–	–	–	–	–	–	0.25	0.5
Streptococcus pyogenes (140)	137 (97.9)	2 (99.3)	1 (100.0)	–	–	–	–	–	–	–	–	–	–	≤0.015	≤0.015
Streptococcus agalactiae (130)	107 (82.3)	22 (99.2)	1 (100.0)	–	–	–	–	–	–	–	–	–	–	≤0.015	0.03
Group C streptococci (18)	16 (88.9)	2 (100.0)	–	–	–	–	–	–	–	–	–	–	–	≤0.015	0.03
Haemophilus influenzae (326)	252 (77.3)	47 (91.7)	14 (96.0)	8 (98.5)	4 (99.7)	0 (99.7)	1 (100.0)	–	–	–	–	–	–	≤0.015	0.03
Haemophilus parainfluenzae (40)	22 (55.0)	4 (65.0)	0 (65.0)	2 (70.0)	3 (77.5)	6 (92.5)	0 (92.5)	1 (95.0)	1 (97.5)	1 (100.0)	–	–	–	≤0.015	0.5
Escherichia coli (674)	6 (0.9)	30 (5.3)	96 (19.6)	90 (32.9)	40 (38.9)	15 (41.1)	9 (42.4)	3 (42.9)	3 (43.3)	5 (44.1)	4 (44.7)	6 (45.5)	367 (100.0)	>32	>32
Non-ESBL phenotype (286)	6 (2.1)	30 (12.6)	95 (45.8)	89 (76.9)	39 (90.6)	13 (95.1)	8 (97.9)	3 (99.0)	2 (99.7)	0 (99.7)	1 (100.0)	–	–	0.12	0.25
ESBL phenotype (388)	–	–	1 (0.3)	1 (0.5)	1 (0.8)	2 (1.3)	1 (1.5)	0 (1.5)	1 (1.8)	5 (3.1)	3 (3.9)	6 (5.4)	367 (100.0)	>32	>32
Klebsiella pneumoniae (447)	3 (0.7)	6 (2.0)	91 (22.4)	82 (40.7)	25 (46.3)	14 (49.4)	7 (51.0)	3 (51.7)	3 (52.3)	3 (53.0)	10 (55.3)	1 (55.5)	199 (100.0)	1	>32
Non-ESBL phenotype (225)	3 (1.3)	6 (4.0)	91 (44.4)	81 (80.4)	24 (91.1)	14 (97.3)	6 (100.0)	–	–	–	–	–	–	0.12	0.25
ESBL phenotype (222)	–	–	–	1 (0.5)	1 (0.9)	0 (0.9)	1 (1.4)	3 (2.7)	3 (4.1)	3 (5.4)	10 (9.9)	1 (10.4)	199 (100.0)	>32	>32
Klebsiella oxytoca (38)	–	2 (5.3)	2 (10.5)	11 (39.5)	6 (55.3)	8 (76.3)	0 (76.3)	0 (76.3)	1 (78.9)	0 (78.9)	0 (78.9)	1 (81.6)	7 (100.0)	0.25	>32
Non-ESBL phenotype (29)	–	2 (6.9)	2 (13.8)	11 (51.7)	6 (72.4)	8 (100.0)	–	–	–	–	–	–	–	0.12	0.5
ESBL phenotype (9)	–	–	–	–	–	–	–	–	1 (11.1)	0 (11.1)	0 (11.1)	1 (22.2)	7 (100.0)	>32	–
Morganella morganii (134)	1 (0.7)	10 (8.2)	26 (27.6)	28 (48.5)	15 (59.7)	10 (67.2)	4 (70.1)	2 (71.6)	3 (73.9)	4 (76.9)	3 (79.1)	3 (81.3)	25 (100.0)	0.25	>32

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit 50% and 90% of the isolates, respectively; MSSA, meticillin-susceptible *S. aureus*; MRSA, meticillin-resistant *S. aureus*; Pen^R, penicillin-resistant; ESBL, extended-spectrum β-lactamase.