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Frequency and antimicrobial susceptibility of bacterial isolates from patients hospitalised with community-acquired skin and skin-structure infection in Europe, Asia and Latin America

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ABSTRACT

Objectives: Ceftaroline fosamil is approved for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs), including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). This study evaluated the frequency and antimicrobial susceptibility of organisms isolated from patients hospitalised with community-acquired (CA) SSSI in Europe, the Asia-Pacific region (APAC) and Latin America (LATAM).

Methods: Isolates ($n = 5120$) were consecutively collected from patients hospitalised with CA-SSSI in 2014–2016 from 63 medical centres in 41 nations, stratified as Western Europe (20 centres/10 nations), Eastern Europe and the Mediterranean region (E-EUR; 16 centres/12 nations), APAC (16 centres/10 nations) and LATAM (11 centres/9 nations). Isolates obtained from outpatients or <48 h after hospitalisation were considered CA. Organisms were tested for susceptibility by reference broth microdilution in a central laboratory.

Results: S. aureus was the most common CA-SSSI organism in all regions, except LATAM, and represented 43.3% of the overall collection. MRSA rates varied from 15.8% (E-EUR) to 21.4% (APAC), being 18.5% overall. In general, 98.9% of *S. aureus* and 94.2% of MRSA isolates were susceptible to ceftaroline, with 99.5% of MRSA isolates inhibited at ≤2 mg/L (0.5% resistant). *Escherichia coli* (14.2%) and β-haemolytic streptococci (BHS) (8.2%) ranked second and third overall, respectively, with wide regional variation. BHS isolates were highly susceptible to ceftaroline (highest MIC, 0.03 mg/L), but exhibited decreased susceptibility to tetracycline and erythromycin.

Conclusion: The frequency and antimicrobial susceptibility of CA-SSSI bacteria varied broadly by geographic region. Ceftaroline exhibited potent activity against *S. aureus* (including MRSA), BHS and ceftriaxone-susceptible Enterobacterales isolates.

1. Introduction

Skin and skin-structure infections (SSSIs) encompass a wide range of clinical presentations, from mild cases of cellulitis and subcutaneous tissue infection to complicated deep-seated infections with systemic signs of sepsis and the presence of complicating co-morbidities, representing a common cause of hospitalisation [1]. The most commonly reported cause of SSSI is *Staphylococcus aureus*, followed by β-haemolytic streptococci (BHS) of Lancefield groups A, C and G, with group B usually more common in diabetic patients and the elderly [2,3].

Ceftaroline is a cephalosporin with broad-spectrum in vitro bactericidal activity against Gram-positive and common Gram-negative pathogens causing SSSIs, including oxacillin (methicillin)-susceptible and –resistant *S. aureus* (MSSA and MRSA, respectively), BHS and non-extended-spectrum β-lactamase (non-ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* [4]. Ceftaroline fosamil is approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the treatment of complicated SSSIs, including those caused by MRSA [5,6].

The SENTRY Antimicrobial Surveillance Program monitors the frequency of occurrence and antimicrobial susceptibility of organisms from various infection types worldwide [7]. In the

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Table 1
List of nations and number of participating centres surveyed in each geographic region.

Western Europe	Eastern Europe	Asia-Pacific region	Latin America
Belgium (1)	Belarus (1)	Australia (5)	Argentina (1)
France (4)	Croatia (1)	Hong Kong (1)	Brazil (2)
Germany (2)	Czech Republic (1)	Japan (1)	Chile (1)
Greece (1)	Hungary (1)	Malaysia (1)	Colombia (1)
Ireland (2)	Israel (1)	New Zealand (2)	Costa Rica (1)
Italy (3)	Poland (1)	Philippines (1)	Ecuador (1)
Portugal (1)	Romania (2)	Singapore (1)	Mexico (2)
Spain (3)	Russia (3)	South Korea (2)	Peru (1)
Sweden (1)	Slovakia (1)	Taiwan (1)	Venezuela (1)
UK (2)	Slovenia (1)	Thailand (1)	
	Turkey (2)		
	Ukraine (1)		

SENTRY Program, bacterial isolates are consecutively collected (one per patient infection episode) according to the infection type and are sent to a monitoring laboratory (JMI Laboratories, North Liberty, IA) where they are tested for antimicrobial susceptibility by reference broth microdilution methods against most antimicrobial agents currently used to treat systemic infections. In this investigation, the frequency and antimicrobial susceptibility of organisms isolated from patients hospitalised with community-acquired (CA) SSSI in Europe, the Asia-Pacific region (APAC) and Latin America (LATAM) were evaluated.

2. Materials and methods

2.1. Organism collection

A total of 5120 bacterial isolates were consecutively collected in 2014–2016 from 63 medical centres distributed as follows (Table 1): Western Europe (W-EUR), 3250 isolates from 20 centres in 10 nations; Eastern Europe and the Mediterranean region (E-EUR), 839 isolates from 16 centres in 12 nations, including Turkey and Israel; and Latin America (LATAM), 365 isolates from 11 centres from 9 nations.

Each participating centre was asked to collect consecutive bacterial isolates from patients hospitalised with SSSI. An isolate obtained from an outpatient or collected <48 h after hospitalisation was considered CA and was included in this investigation.

2.2. Antimicrobial susceptibility testing methods

Broth microdilution tests were conducted according to Clinical and Laboratory Standards Institute (CLSI) documents to determine the susceptibility of the isolates to ceftaroline and numerous comparator antimicrobials used to treat patients with SSSI [8]. Minimum inhibitory concentration (MIC) panels were prepared at JMI Laboratories (2015–2016) or were manufactured by Thermo Fisher Scientific (Cleveland, OH) (2014).

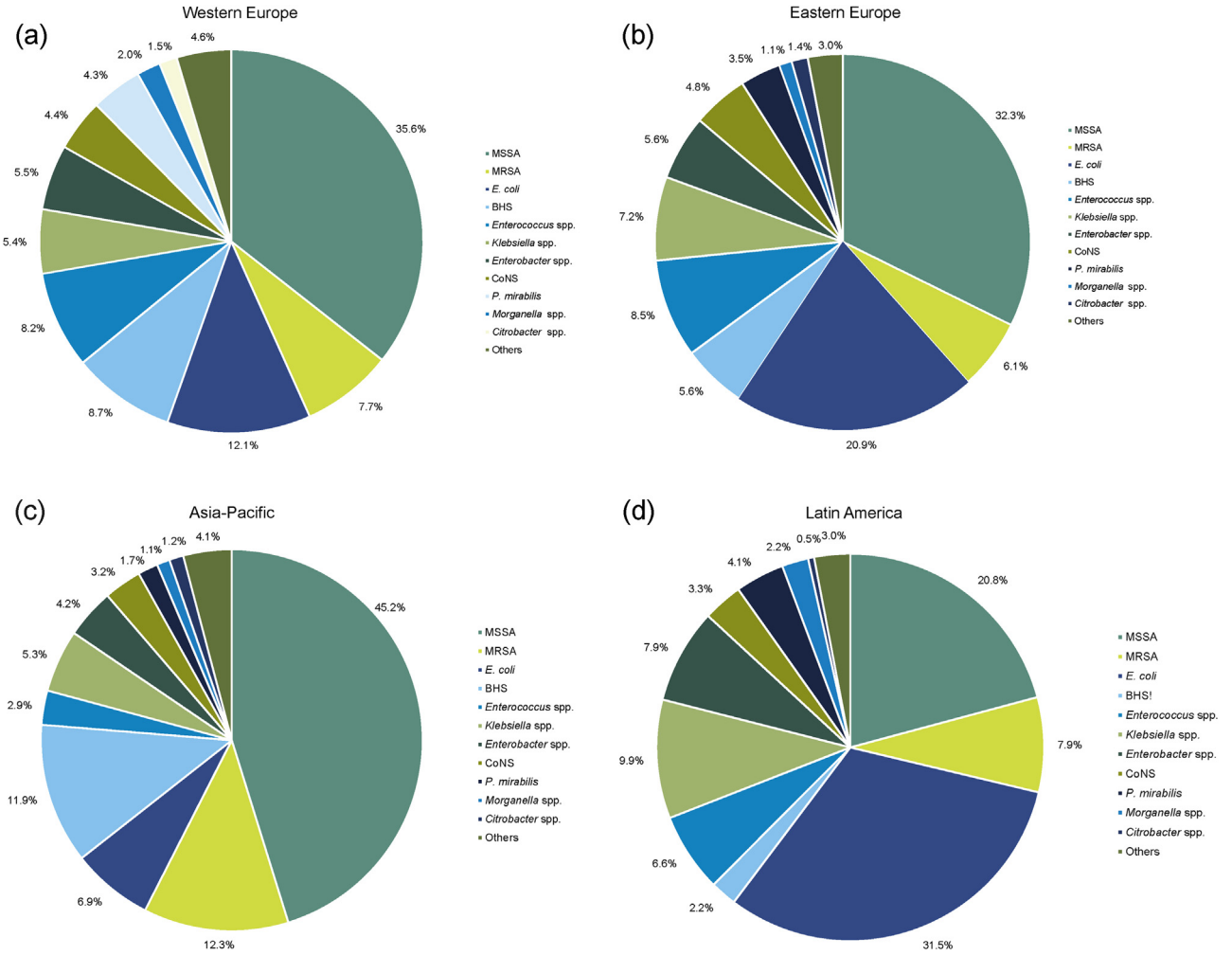

Fig. 1. Frequency of occurrence of organisms isolated from patients hospitalised with community-acquired skin and skin-structure infections stratified by geographic region. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; BHS, β-haemolytic streptococci; CoNS, coagulase-negative staphylococci.

Table 2
Antimicrobial activity of ceftaroline tested against the main organisms and organism groups of isolates from all geographic regions combined.

Organism/organism group (no. of isolates)	No. of isolates (cumulative %) at MIC (in mg/L) of:													MIC (mg/L)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>[a]	MIC_{50}	MIC_{90}
Staphylococcus aureus (2216)			13 (0.6)	227 (10.8)	1530 (79.9)	262 (91.7)	160 (98.9)	22 (99.9)	2 (100.0)					0.25	0.5
Methicillin-susceptible (1805)			13 (0.7)	227 (13.3)	1516 (97.3)	49 (100.0)								0.25	0.25
Methicillin-resistant (411)				0 (0.0)	14 (3.4)	213 (55.2)	160 (94.2)	22 (99.5)	2 (100.0)					0.5	1
β-Haemolytic streptococci (418)	413 (98.8)	5 (100.0)												≤0.015	≤0.015
Enterococcus spp. (382)					7[b] (1.8)	12 (5.0)	78 (25.4)	132 (59.9)	28 (67.3)	18 (72.0)			107 (100.0)	2	>8
E. faecalis (277)					4[b] (1.4)	5 (3.2)	77 (31.0)	130 (78.0)	27 (87.7)	18 (94.2)			16 (100.0)	2	8
Coagulase-negative staphylococci (215)			62[c] (28.8)	28 (41.9)	68 (73.5)	37 (90.7)	13 (96.7)	7 (100.0)						0.25	0.5
Methicillin-susceptible (116)			61[c] (52.6)	21 (70.7)	30 (96.6)	4 (100.0)								≤0.06	0.25
Methicillin-resistant (99)		0 (0.0)	1 (1.0)	7 (8.1)	38 (46.5)	33 (79.8)	13 (92.9)	7 (100.0)						0.5	1
Viridans group streptococci (66)	35 (53.0)	24 (89.4)	3 (93.9)	2 (97.0)	0 (97.0)	2 (100.0)								≤0.015	0.06
Enterobacterales (1822)	22 (1.2)	97 (6.5)	388 (27.8)	388 (49.1)	224 (61.4)	140 (69.1)	89 (74.0)	41 (76.2)	28 (77.8)	21 (78.9)	22 (80.1)	35 (82.1)	327 (100.0)	0.25	>32
Escherichia coli (729)	15 (2.1)	59 (10.2)	192 (36.5)	162 (58.7)	72 (68.6)	35 (73.4)	23 (76.5)	11 (78.1)	9 (79.3)	5 (80.0)	6 (80.8)	3 (81.2)	137 (100.0)	0.12	>32
Ceftriaxone-susceptible (572)	15 (2.6)	59 (12.9)	192 (46.5)	162 (74.8)	72 (87.4)	35 (93.5)	21 (97.2)	7 (98.4)	4 (99.1)	2 (99.5)	0 (99.5)	1 (99.7)	2 (100.0)	0.12	0.5
Klebsiella spp. (305)	2 (0.7)	9 (3.6)	69 (26.2	52 (43.3)	33 (54.1)	21 (61.0)	4 (62.3)	1 (62.6)	3 (63.6)	6 (65.6)	0 (65.6)	3 (66.6)	102 (100.0)	0.25	>32
Ceftriaxone-susceptible (198)	2 (1.0)	9 (5.6)	69 (40.4)	52 (66.7)	33 (83.3)	21 (93.9)	4 (96.0)	1 (96.5)	2 (97.5)	4 (99.5)	0 (99.5)	0 (99.5)	1 (100.0)	0.12	0.5
Enterobacter spp. (282)	0 (0.0)	4 (1.4)	19 (8.2)	67 (31.9)	64 (54.6)	23 (62.8)	12 (67.0)	4 (68.4)	8 (71.3)	2 (72.0)	9 (75.2)	19 (81.9)	51 (100.0)	0.25	>32
Ceftriaxone-susceptible (186)		4 (2.2)	19 (12.4)	66 (47.8)	64 (82.3)	19 (92.5)	9 (97.3)	1 (97.8)	4 (100.0)					0.25	0.5
Proteus mirabilis (193)	0 (0.0)	10 (5.2)	73 (43.0)	51 (69.4)	15 (77.2)	6 (80.3)	10 (85.5)	1 (86.0)	2 (87.0)	3 (88.6)	4 (90.7)	1 (91.2)	17 (100.0)	0.12	16
Serratia marcescens (83)				0 (0.0)	6 (7.2)	33 (47.0)	25 (77.1)	13 (92.8)	1 (94.0)	1 (95.2)	2 (97.6)	1 (98.8)	1 (100.0)	1	2
Morganella morganii (90)	0 (0.0)	9 (10.0)	13 (24.4)	27 (54.4)	15 (71.1)	6 (77.8)	4 (82.2)	2 (84.4)	0 (84.4)	1 (85.6)	0 (85.6)	2 (87.8)	11 (100.0)	0.12	>32
Citrobacter spp. (70)	0 (0.0)	2 (2.9)	17 (27.1)	26 (64.3)	12 (81.4)	9 (94.3)	0 (94.3)	0 (94.3)	0 (94.3)	1 (95.7)	0 (95.7)	1 (97.1)	2 (100.0)	0.12	0.5
Other Enterobacterales (70)	5 (7.1)	4 (12.9)	5 (20.0)	3 (24.3)	7 (34.3)	7 (44.3)	11 (60.0)	9 (72.9)	5 (80.0)	2 (82.9)	1 (84.3)	5 (91.4)	6 (100.0)	1	32

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MICs required to inhibit 50% and 90% of the isolates, respectively.
[a] Greater than the highest dilution tested.
[b] Isolates with ceftaroline MIC of ≤0.25 mg/L.
[c] Isolates with ceftaroline MIC of ≤0.06 mg/L.

Table 3
Activity of ceftaroline and comparator antimicrobial agents when tested against main organisms isolated from patients hospitalised with community-acquired skin and skin-structure infections.

Organisms/antimicrobial agent	MIC (mg/L)		All regions combined	W-EUR	E-EUR	APAC	LATAM
	MIC_{50}	MIC_{90}	% susceptible (no. of isolates tested)[a]				
Staphylococcus aureus			(2216)	(1406)	(322)	(383)	(105)
Ceftaroline	0.25	0.5	98.9	99.0	99.1	98.7	98.1
Ceftriaxone	4	>8	81.5	82.3	84.2	78.6	72.4
Oxacillin	0.5	>2	81.5	82.3	84.2	78.6	72.4
Azithromycin	0.5	>4	74.5	72.6	67.9	81.4	76.2
Erythromycin	0.25	>8	76.5	75.3	73.3	83.8	75.2
Clindamycin	≤0.25	≤0.25	93.6	93.4	93.5	94.5	93.3
Tetracycline	≤0.5	≤0.5	92.7	94.2	86.0	92.7	94.3
Doxycycline	≤0.06	0.12	98.3	98.6	98.1	96.9	100.0
Levofloxacin	0.25	>4	85.3	82.8	87.6	90.6	92.4
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0
Daptomycin	0.25	0.5	100.0	100.0	100.0	100.0	100.0
SXT	≤0.5	≤0.5	99.4	99.6	99.7	98.2	99.0
Tigecycline[b]	0.06	0.12	100.0	100.0	100.0	100.0	100.0
Vancomycin	0.5	1	100.0	100.0	100.0	100.0	100.0
MSSA			(1805)	(1157)	(271)	(301)	(76)
Ceftaroline	0.25	0.25	100.0	100.0	100.0	100.0	100.0
Ceftriaxone	4	4	100.0	100.0	100.0	100.0	100.0
Azithromycin	0.5	>4	83.0	82.7	78.8	86.7	77.5
Erythromycin	0.25	>8	83.9	83.2	83.4	89.0	75.0
Clindamycin	≤0.25	≤0.25	98.0	97.5	99.3	98.7	97.4
Tetracycline	≤0.5	≤0.5	95.2	96.4	89.7	95.3	97.4
Doxycycline	≤0.06	0.12	99.3	99.3	98.9	99.7	100.0
Levofloxacin	0.25	0.25	95.2	95.0	95.9	95.0	97.4
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0
Daptomycin	0.5	0.5	100.0	100.0	100.0	100.0	100.0
SXT	≤0.5	≤0.5	99.7	99.7	100.0	99.7	100.0
Tigecycline[b]	0.06	0.12	100.0	100.0	100.0	100.0	100.0
Vancomycin	0.5	1	100.0	100.0	100.0	100.0	100.0
MRSA			(411)	(249)	(51)	(82)	(29)
Ceftaroline	0.5	1	94.2	94.4	94.1	93.9	93.1
Azithromycin	>4	>4	39.0	27.9	30.0	62.9	50.0
Erythromycin	>8	>8	44.0	38.6	19.6	64.6	75.9
Clindamycin	≤0.25	>2	74.5	74.3	62.7	79.3	82.8
Tetracycline	≤0.5	>8	81.8	83.9	66.7	82.9	86.2
Doxycycline	≤0.06	2	93.9	95.6	94.1	86.6	100.0
Levofloxacin	4	>4	41.6	26.1	43.1	74.4	79.3
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0
Daptomycin	0.25	0.5	100.0	100.0	100.0	100.0	100.0
SXT	≤0.5	≤0.5	97.8	99.6	98.0	92.7	96.6
Tigecycline[b]	0.06	0.12	100.0	100.0	100.0	100.0	100.0
Vancomycin	0.5	1	100.0	100.0	100.0	100.0	100.0
β-Haemolytic streptococci			(418)	(284)	(47)	(79)	(8)
Ceftaroline	≤0.015	≤0.015	100.0	100.0	100.0	100.0	100.0
Ceftriaxone	≤0.06	≤0.06	100.0	100.0	100.0	100.0	100.0
Penicillin	≤0.06	≤0.06	100.0	100.0	100.0	100.0	100.0
AMC	≤1	≤1	100.0	100.0	100.0	100.0	100.0
Azithromycin	0.12	32	81.9	84.3	76.0	76.9	80.0
Erythromycin	≤0.12	>4	82.8	84.5	78.7	79.7	75.0
Clindamycin	≤0.25	0.5	90.0	90.1	89.4	89.9	87.5
Tetracycline	≤0.5	>8	60.3	65.2	44.7	54.4	37.5
Levofloxacin	0.5	1	98.8	100.0	97.9	96.2	87.5
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0
Daptomycin	0.12	0.25	100.0	100.0	100.0	100.0	100.0
Tigecycline[b]	0.03	0.06	100.0	100.0	100.0	100.0	100.0
Vancomycin	0.25	0.5	100.0	100.0	100.0	100.0	100.0
Enterobacterales			(1822)	(1105)	(353)	(149)	(215)
Ceftaroline	0.25	>32	69.1	73.6	62.0	65.8	60.0
Ceftriaxone	≤0.06	>8	76.6	82.7	67.4	69.8	65.1
Ceftazidime	0.25	32	82.5	88.0	72.8	79.2	72.6
Cefepime	≤0.5	16	84.3	89.9	74.8	83.9	72.0
Aztreonam	≤0.12	>16	81.7	87.6	71.7	77.9	70.2
SAM	16	>32	39.1	40.7	36.4	35.6	37.7
TZP	2	32	89.1	91.0	86.0	85.8	86.5
Imipenem	≤0.12	2	86.5	85.2	87.0	87.8	91.6
Meropenem	0.03	0.06	98.2	98.8	96.6	98.0	98.1
Ciprofloxacin	≤0.03	>4	75.3	79.7	68.0	77.7	62.8
Levofloxacin	≤0.12	>4	78.4	82.5	72.2	79.1	66.5
Gentamicin	≤1	>8	86.3	90.6	79.3	86.6	75.3
Amikacin	2	4	98.6	98.9	97.7	98.0	99.1

Table 3 (*Continued*)

Organisms/antimicrobial agent	MIC (mg/L)		All regions combined	W-EUR	E-EUR	APAC	LATAM
	MIC_{50}	MIC_{90}	% susceptible (no. of isolates tested)[a]				
Tigecycline[b]	0.25	2	97.6	97.2	98.3	98.7	97.7
Colistin	≤0.5	>8	73.7	69.8	80.0	74.5	82.7

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MICs required to inhibit 50% and 90% of the isolates, respectively; W-EUR, Western Europe; E-EUR, Eastern Europe; APAC, Asia-Pacific region; LATAM, Latin America; SXT, trimethoprim/sulfamethoxazole; MSS, MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; AMC, amoxicillin/clavulanic acid; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam.

[a] Criteria as published by CLSI [9].

[b] Breakpoints from FDA package insert revised 12/2014.

S. aureus and Enterobacterales were tested in cation-adjusted Mueller–Hinton broth (CA-MHB), and streptococci were tested in CA-MHB supplemented with 2.5–5% lysed horse blood according to CLSI document M07 [8]. Quality control (QC) strains included *S. aureus* ATCC 29213, *Streptococcus pneumoniae* ATCC 49619 and *E. coli* ATCC 25922 and 35218. Susceptibility percentages and QC results validation were based on the CLSI M100 document [9].

3. Results

S. aureus was the most common CA-SSSI organism in W-EUR (43.3%), E-EUR (38.4%) and APAC (57.5%), representing 43.3% of the overall collection (Fig. 1). *E. coli* was the most common organism in LATAM (31.5%) and was the second most common in the other regions, with prevalences varying from 20.9% in E-EUR to 6.9% in the APAC region. BHS ranked second in the APAC region (11.9%), third in W-EUR (8.7%), fifth in E-EUR (5.6%), eighth in LATAM (2.2%) and third overall (8.2%). *Enterococcus* spp. (7.5%), *Klebsiella* spp. (6.0%) and *Enterobacter* spp. (5.5%) ranked fourth, fifth and sixth overall, respectively, but, the rank order varied among geographic regions (Fig. 1).

Ceftaroline was very active against *S. aureus* overall ($MIC_{50/90}$, 0.25/0.5 mg/L; 98.9% susceptible). When tested against MSSA, ceftaroline ($MIC_{50/90}$, 0.25/0.25 mg/L) was 16-fold more potent than ceftriaxone ($MIC_{50/90}$, 4/4 mg/L), 4-fold more active than linezolid ($MIC_{50/90}$, 1/1 mg/L) and 2–4-fold more active than vancomycin ($MIC_{50/90}$, 0.5/1 mg/L). Ceftaroline activity against MSSA (100.0% susceptible) was comparable with that observed for daptomycin (100.0% susceptible), vancomycin (100.0% susceptible), tigecycline (100.0% susceptible), trimethoprim/sulfamethoxazole (99.7% susceptible) and clindamycin (98.0% susceptible). The highest ceftaroline MIC among MSSA strains was only 0.5 mg/L, and 97.3% of strains were inhibited at a ceftaroline MIC of ≤0.25 mg/L (Tables 2 and 3).

The overall MRSA rate was 18.5%, ranging from 15.8% in E-EUR to 21.4% in APAC (Table 3). MRSA represented 8.0% of all isolates collected from CA-SSSI. When tested against MRSA, ceftaroline MICs ranged from 0.25 mg/L to 4 mg/L ($MIC_{50/90}$, 0.5/1 mg/L) (Table 2). Overall, 94.2% of MRSA isolates were susceptible to ceftaroline and only 0.5% were ceftaroline-resistant (Tables 2 and 3). MRSA susceptibility to macrolides and fluoroquinolones varied substantially among the geographic regions. For example, susceptibility to erythromycin was 38.6% in W-EUR, 19.6% in E-EUR, 64.6% in the APAC region and 75.9% in LATAM; and susceptibility to levofloxacin was 26.1% in W-EUR, 43.1% in E-EUR, 74.4% in the APAC region and 79.3% in LATAM (Table 3).

Against BHS, ceftaroline exhibited comparable activity ($MIC_{50/90}$, ≤0.015/≤0.015 mg/L) to that of penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L) and tigecycline ($MIC_{50/90}$, 0.03/0.06 mg/L) (Tables 2 and 3). The highest ceftaroline MIC was only 0.03 mg/L (Table 2). Decreased susceptibility was observed for tetracycline (60.3% susceptible), azithromycin (81.9% susceptible) and erythromycin (82.8% susceptible) (Table 3). The vancomycin resistance rate among enterococci was 8.4% overall, ranging from 2.8% (E-EUR) to 10.5% (APAC) (data not shown), and ceftaroline exhibited limited activity against these organisms ($MIC_{50/90}$, 2/>8 mg/L) (Table 2).

Coagulase-negative staphylococci (CoNS) strains [46.0% methicillin (oxacillin)-resistant] were very susceptible to ceftaroline ($MIC_{50/90}$, 0.25/0.5 mg/L) (Table 2). The highest ceftaroline MIC among CoNS strains was 2 mg/L, and 96.7% of isolates were inhibited at a ceftaroline MIC of ≤1 mg/L (Table 2).

Ceftaroline and tigecycline ($MIC_{50/90}$, ≤0.015/0.06 mg/L for both compounds) were the most active agents (lower MICs) tested against the viridans group streptococci. Ceftaroline was 4-fold more active than ceftriaxone (MIC_{90}, 0.25 mg/L) and 8–16-fold more potent than linezolid (MIC_{90}, 1 mg/L), vancomycin (MIC_{90}, 0.5 mg/L) and daptomycin (MIC_{90}, 0.5 mg/L) based on MIC_{90} values (data not shown).

When tested against Enterobacterales isolates from SSSI, ceftaroline susceptibility rates varied from 73.6% in W-EUR to 60.0% in LATAM (Table 3). Ceftaroline exhibited good activity against ceftriaxone-susceptible isolates of *E. coli* ($MIC_{50/90}$, 0.12/0.5 mg/L; 93.5% susceptible), *Klebsiella* spp. ($MIC_{50/90}$, 0.12/0.5 mg/L; 93.9% susceptible) and *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.5 mg/L; 92.5% susceptible), but had limited activity against ceftriaxone-non-susceptible isolates (Table 2). Among Enterobacterales isolates overall, meropenem susceptibility ranged from 98.8% in W-EUR to 96.6% in E-EUR (Table 3), and susceptibility to levofloxacin and gentamicin were highest in W-EUR (82.5% and 90.6%, respectively) and lowest in LATAM (66.5% and 75.3%, respectively) (Table 3).

4. Discussion

In this investigation, the in vitro activity of ceftaroline and many comparator agents tested against bacterial isolates from patients hospitalised with CA-SSSI in numerous medical centres throughout Europe, Asia and Latin America were evaluated. The frequency of bacteria isolated from patients with CA-SSSI varied broadly by geographic region, and potent activity of ceftaroline was documented against the most common organisms isolated in all geographic regions. Ceftaroline activity against *S. aureus* was comparable with that of vancomycin and linezolid, whereas activity against BHS was more similar to that of penicillin and ceftriaxone. Ceftaroline was also highly potent against CoNS, including oxacillin-resistant isolates, and viridans group streptococci, including ceftriaxone-non-susceptible isolates. The activity of ceftaroline tested against *E. coli* and *Klebsiella* spp. isolates was most similar to that of ceftriaxone and ceftazidime; however, the activity of all these cephalosporins was compromised against those isolates exhibiting an ESBL phenotype or resistance to carbapenems (imipenem or meropenem).

It is important to note that *S. aureus* had an overall MRSA rate of 18.5% and represented 43.3% of the bacterial isolates collected from patients with CA-SSSI and was very susceptible to ceftaroline, with 98.9% of isolates being susceptible and 99.9% inhibited at ≤2 mg/L. Current CLSI, European Committee on Antimicrobial Susceptibility Testing (EUCAST) and FDA breakpoints for ceftaroline against *S. aureus*, including MRSA when treating SSSI, are susceptible at ≤1 mg/L, intermediate at 2 mg/L and resistant at ≥4 mg/L, and were established based on a ceftaroline fosamil dosage of 600 mg every 12 h [5,6,9,10]. However, a higher dosage of 600 mg every 8 h (q8 h) by 2-h infusion has been evaluated in a phase 3 prospective, double-blind, active-comparator clinical trial called COVERS (ClinicalTrials.gov. ID: NCT01499277) [11]. The results of the COVERS study demonstrated that ceftaroline fosamil 600 mg q8 h was well tolerated and non-inferior to vancomycin plus aztreonam in terms of clinical cure rates. The results of this study also showed that ceftaroline fosamil 600 mg q8 h by 2-h infusion can provide sufficient exposure for *S. aureus* with a ceftaroline MIC of 4 mg/L [11,12]. The ceftaroline 600 mg q8 h dosage has been approved in Europe (Western and Eastern European countries) and is being reviewed in countries in Asia, Latin America and Africa. This higher dosage should provide appropriate coverage for MRSA infections in all geographic regions evaluated in this investigation.

The limitations of the study should be considered when interpreting these data. The main limitation of this investigation was the definition used to designate a CA isolate, i.e. 'an isolate obtained from an outpatient or collected <48 h after hospitalisation', since it does not consider prior patient exposure to healthcare and other risk factors that could be used to differentiate community-acquired from healthcare-associated. Despite this limitation, the results presented here provide valuable information. In summary, ceftaroline showed excellent in vitro activity when tested against a large collection ($n = 5120$) in a longitudinal survey (2014–2016) of contemporary bacterial isolates from patients hospitalised with CA-SSSIs across 41 nations in Europe, the APAC region and Latin America. The in vitro data presented here coupled with pharmacokinetic/pharmacodynamic and clinical data reported by other investigators indicate that ceftaroline is a valuable agent for treatment of SSSIs, including those caused by MRSA.

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Competing interests

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Ethical approval

Not required.

References

[1] Garau J, Blasi F, Medina J, McBride K, Ostermann H, REACH Study Group. Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study. BMC Infect Dis 2015;15:78, doi:http://dx.doi.org/10.1186/s12879-015-0822-2.
[2] 1Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother 2010;65(Suppl 3), doi:http://dx.doi.org/10.1093/jac/dkq302 iii35-44.
[3] Russo A, Concia E, Cristini F, De Rosa FG, Esposito S, Menichetti F, et al. Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. Clin Microbiol Infect 2016;22(Suppl 2):S27–36, doi:http://dx.doi.org/10.1016/S1198-743X(16)30095-7.
[4] Frampton JE. Ceftaroline fosamil: a review of its use in the treatment of complicated skin and soft tissue infections and community-acquired pneumonia. Drugs 2013;73:1067–94, doi:http://dx.doi.org/10.1007/s40265-013-0075-6.
[5] Zinforo®. Zinforo™ prescribing information. 2012. . Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm.
[6] Teflaro®. Teflaro® package insert. New York, NY: Allergan; 2016.
[7] Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized with pneumonia in United States and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. Int J Antimicrob Agents 2014;43:328–34.
[8] Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. CLSI standard M07. 11th ed. Wayne, PA: CLSI; 2018.
[9] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. CLSI supplement M100. 28th ed. Wayne, PA: CLSI; 2018.
[10] European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, January 2018. EUCAST; 2018. . [Accessed January 2018] http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf.
[11] Das S, Li J, Gonzalez J, Melnick D, Zhou D, Iaconis JP, et al. Ceftaroline fosamil 600 mg every 8 h for the treatment of ABSSSI due to *Staphylococcus aureus* with ceftaroline MICs of 4 mg/L. 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 17–21 September 2015. [poster A-455].
[12] Li J, Singh R, Ambler JE. Probability of target attainment (PTA) and pharmacokinetic/pharmacodynamic (PK/PD) breakpoint for ceftaroline fosamil 600 mg every 12 h and every 8 h against Staphylococcus aureus. 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 25-28 April 2015. [poster P1384].