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ORIGINAL RESEARCH

In vitro Activity of Ceftaroline Against Isolates of Gram-Positive Bacteria from Patients with Bloodstream Infections Collected as a Part of ATLAS Between 2017 and 2020

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Purpose: To assess the in vitro activity of ceftaroline and a panel of comparator agents against isolates of Gram-positive bacteria, including *Staphylococcus aureus, Streptococcus pneumoniae*, β-hemolytic streptococci, and coagulase-negative staphylococci (CoNS) from blood collected in Africa and Middle East (AfME), Asia Pacific (APAC), Europe, Latin America (LATAM), and North America from 2017 to 2020 as a part of the Antimicrobial Testing Leadership and Surveillance (ATLAS) program.

Methods: Susceptibility and minimum inhibitory concentration were determined using broth microdilution for all antimicrobial agents by a central reference laboratory according to the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.

Results: Ceftaroline showed good activity (susceptibility ≥89.8%, MIC_{90} 0.008–2 mg/L) against all Gram-positive isolates tested. All isolates of methicillin-susceptible *S. aureus*, penicillin-susceptible *S. pneumoniae, S. agalactiae, S. dysgalactiae*, and *S. pyogenes* were susceptible to ceftaroline (MIC_{90} 0.008–0.25 mg/L). Ceftaroline susceptibility for MRSA isolates was 89.8% globally (MIC_{90} 2 mg/L). Among the comparator agents, all isolates were susceptible to vancomycin, except *S. epidermis* (susceptibility, 99.9%). Among other agents, daptomycin, linezolid, and tigecycline showed potent activity (susceptibility ≥97.9%, MIC_{90} 0.03–2 mg/L) against all isolates tested.

Conclusion: Ceftaroline showed potent in vitro activity against global bloodstream isolates of Gram-positive bacteria collected between 2017 and 2020. Monitoring and surveillance of global as well as regional longitudinal trends of resistance rates among Gram-positive isolates causing bloodstream infections are important to limit the spread of AMR, establish stewardship measures, and manage and appropriately treat infections.

Keywords: ATLAS, bloodstream infections, ceftaroline, Gram-positive bacteria, surveillance

Introduction

Bloodstream infections (BSIs) are often difficult to treat and are associated with high morbidity, mortality, and social and economic burden.[1,2] BSIs are responsible for 40% of community-acquired and hospital-acquired sepsis and about 20% of all intensive care unit (ICU)-acquired infections.[3] Over 50% of all BSIs are caused by Gram-positive bacteria, including *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and *Streptococcus* spp. including *Streptococcus pneumoniae* and β-hemolytic streptococci.[1,3,4] A global SENTRY surveillance study assessing organisms causing BSIs from 1997 to 2016 reported that *S. aureus* accounted for 20.7%, *S. epidermis* 3.8%, and *S. pneumoniae* 2.8% of BSIs.[5] Another study that assessed disability-adjusted-life-years (DALY) for infections caused by antibiotic-resistant bacteria in Europe reported a median DALY (per 100,000 population) percentage of 63.9 for methicillin-resistant *S. aureus* (MRSA), 49.1% for penicillin-resistant *S. pneumoniae* (PRSP), and 77.4% for penicillin-and-macrolide-resistant *S. pneumoniae* causing BSIs.[6]

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Treatment and management of patients with BSIs involve accurate diagnosis to identify the infection source, choosing the appropriate antibacterial for treatment, duration of therapy, and effective source control.[7] Furthermore, there is a lack of evidence on effective treatment options for Gram-positive BSI; current treatment approaches are mostly based on observational or non-randomized trials.[7–9] Hence, treatment of BSIs, especially those caused by resistant strains of Gram-positive bacteria, is challenging.

Ceftaroline, the active form of ceftaroline fosamil, is a cephalosporin with a broad in vitro activity against Gram-positive bacteria including MRSA and PRSP.[10] Ceftaroline mediates its antibacterial activity by binding to penicillin-binding proteins to inhibit cell wall synthesis leading to cell lysis and death.[10] Ceftaroline has been approved by the Food and Drug Administration and European Medicine Agency for acute bacterial skin and skin structure infections (ABSSSI)/ complicated skin and skin structure infections (cSSTI) and community-acquired bacterial pneumonia (CAP) in both adult and pediatric patients.[11,12] Ceftaroline has not been approved for treatment of BSIs by the EMA. However, ceftaroline has been approved for treatment of CAP with concurrent bacteremia caused by *S. pneumoniae*.[11] Notably, ceftaroline has previously been used as a salvage therapy for BSI caused by MRSA.[13,14] Interestingly, a retrospective observational study in the United States (US) assessing the use of ceftaroline outside of its approved indications over two years (2011–2013) showed that the most common off-label use of ceftaroline was for the treatment of BSIs.[15] Furthermore, it was observed that ceftaroline was most frequently used following disease progression on prior antibiotic therapy.[15] These reports indicate that ceftaroline could be effective for the treatment of BSIs.

Recently, there has been an emergence and spread of drug-resistant bacteria due to increase in the use of antibiotics.[2,5] Considering the limited treatment options for BSI, especially those caused by resistant strains, it is important to monitor the resistance trends of these organisms to antimicrobials. There have been only limited number of studies assessing the activity of ceftaroline against Gram-positive bacteria causing BSI.[16,17] Hence, to assess the activity of ceftaroline against a recent collection of Gram-positive bacteria from BSI, we conducted this in vitro study and tested ceftaroline and a panel of comparator agents against isolates of Gram-positive bacteria, including *S. aureus, S. pneumoniae*, β-hemolytic streptococci (*S. agalactiae, S. dysgalactiae*, and *S. pyogenes*), and coagulase-negative staphylococci (CoNS) from blood collected in Africa and Middle East (AfME), Asia Pacific (APAC), Europe, Latin America (LATAM), and North America from 2017 to 2020 as a part of the Antimicrobial Testing Leadership and Surveillance (ATLAS) program.[18]

Methods

Bacterial Isolates

Non-duplicate, clinically significant isolates (single isolate per patient) of *S. aureus, S. pneumoniae, S. agalactiae, S. dysgalactiae, S. pyogenes*, and CoNS, which included isolates of *S. capitis, S. epidermis, S. haemolyticus, S. hominis, S. lugdunensis, S. saprophyticus*, and *S. simulans*, independent of age, sex, previous antimicrobial use, or medical history were collected each year in different sites across regions worldwide (AfME, APAC, Europe, LATAM, and North America) from hospitalized patients with bloodstream infections between 2017 and 2020. Every year, each participating site was requested to collect a pre-defined number of isolates of selected species as a part of the ATLAS protocol. The isolates were identified at each site and shipped to a central reference laboratory (International Health Management Associates, Inc. Schaumburg, IL, USA) for species confirmation and antimicrobial susceptibility. Species confirmation was done using matrix-assisted laser desorption ionization time-of-flight spectrometry (Bruker Biotyper MALDI-TOF, Bruker Daltonics, Billerica, MA, USA).

Antimicrobial Susceptibility Testing

Susceptibility and minimum inhibitory concentrations (MIC) of isolates were determined using broth microdilution methodology for ceftaroline and a panel of comparator antimicrobial agents – ceftriaxone, daptomycin, erythromycin, levofloxacin, linezolid, minocycline, tigecycline, trimethoprim-sulfamethoxazole (TMP-SMX), and vancomycin. Antimicrobial susceptibility testing was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[19] MICs were interpreted according to CLSI guidelines[20] and version 13.0 of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables.[21] For tigecycline, no susceptibility breakpoints are defined per CLSI, hence FDA approved breakpoints were used.[22] For *S. aureus*, EUCAST revised the clinical

breakpoints for ceftaroline in 2017 to susceptible ≤1 mg/L and resistant >1 mg/L.[23] Not all antimicrobials were tested in each year of the surveillance, hence varying numbers of isolates were recorded against the different antimicrobials. Methicillin resistance for each *S. aureus* isolate was determined using the oxacillin MIC method (MIC ≥ 4 mg/L confirmed methicillin resistance) per CLSI guidelines.[20] *S. pneumoniae* were classified as penicillin-susceptible or -resistant per the CLSI MIC definitions for oral penicillin V (0.12–1 and ≥2 mg/mL).[20] MIC breakpoints for ceftaroline in β-hemolytic streptococci (*S. agalactiae, S. dysgalactiae, and S. pyogenes*) have not been defined by EUCAST, specifying that the susceptibility to ceftaroline can be inferred from testing benzyl penicillin.[21] For CoNS, both CLSI and EUCAST have not established breakpoints for ceftaroline, hence only MIC data have been presented.[17]

Results

Distribution of Isolates

A total of 16,104 isolates of Gram-positive bacteria from 319 sites in 60 countries including, *S. aureus* (N = 7,373, 306 sites), *S. pneumoniae* (N = 2,755, 253 sites), *S. agalactiae* (N = 801, 192 sites), *S. dysgalactiae* (N = 316, 136 sites), *S. pyogenes* (N = 704, 185 sites), and CoNS (N = 4,155, 275 sites) from blood were collected in different regions between 2017 and 2020 (Supplementary Table 1).

Among the *S. aureus* isolates, 69.5% (5,126/7,373) were MSSA, and 30.5% (2,247/7,373) were MRSA globally. Among the different regions, the highest proportion of MRSA isolates were collected in APAC (38.8%, 474/1223) and the lowest were collected in AfME (24.0%, 126/525; Table 1).

Among *S. pneumoniae* isolates, 76.1% were penicillin-susceptible *Streptococcus pneumoniae* (PSSP; 2,097/2,755) and 9.9%/4.1% (CLSI/EUCAST) were PRSP (CLSI, 273/2,755; EUCAST, 112/2755). Among the different regions, the highest proportion of PRSP isolates was collected in LATAM (CLSI, 22.1%, 45/204; EUCAST 10.8%, 22/204), and the lowest proportion was collected in North America (CLSI, 3.3%, 13/400; EUCAST, 1%, 4/400; Table 1).

Among the CoNS isolates collected, majority were identified as *S. epidermis* (56.0%, 2,326/4,155) and *S. haemolyticus* (38.9%, 1,615/4,155). The rest (5.1%) were identified as *S. capitis* (1.4%, 57/4,155), *S. hominis* (3.1%, 130/4,155), *S. lugdunensis* (0.3%, 13/4155), *S. saprophyticus* (0.3%, 12/4,155), and *S. simulans* (0.05%, 2/4,155).

Table 1 Distribution of Gram-Positive Isolates from Blood Collected Globally and Across Different Regions in 2017–2020

Organisms/ Region	Global	AfME	APAC	Europe	LATAM	North America
S. aureus (N)	7373	525	1223	3458	1327	840
MRSA [n (% of N)]	2247 (30.5%)	126 (24.0%)	474 (38.8%)	849 (24.6%)	502 (37.8%)	296 (35.2%)
MSSA [n (% of N)]	5126 (69.5%)	399 (76.0%)	749 (61.2%)	2609 (75.4%)	825 (62.2%)	544 (64.8%)
S. pneumoniae (N)	2755	224	336	1591	204	400
PRSP (CLSI) [n (% of N)]	273 (9.9%)	36 (16.1%)	71 (21.1%)	108 (6.8%)	45 (22.1%)	13 (3.3%)
PRSP (EUCAST) [n (% of N)]	112 (4.1%)	12 (5.4%)	24 (7.1%)	50 (3.1%)	22 (10.8%)	4 (1.0%)
PSSP [n (% of N)]	2097 (76.1%)	148 (66.1%)	196 (58.3%)	1310 (82.3%)	103 (50.5%)	340 (85.0%)
S. agalactiae (N)	801	52	145	349	84	171
S. dysgalactiae (N)	316	16	67	140	46	47

(*Continued*)

Table 1 (Continued).

Organisms/ Region	Global	AfME	APAC	Europe	LATAM	North America
S. pyogenes (N)	704	57	101	341	82	123
CoNS (N)[a]	4155	473	671	1943	638	430
S. epidermis [n (% of N)]	2326 (56.0%)	210 (44.4%)	332 (49.5%)	1130 (58.2%)	379 (59.4%)	275 (64.0%)
S. haemolyticus [n (% of N)]	1615 (38.9%)	215 (45.5%)	281 (41.9%)	738 (38.0%)	231 (36.2%)	150 (34.9%)

Notes: [a]Includes isolates of *S. capitis* (N=57), *S. epidermis* (N=2326), *S. haemolyticus* (N=1615), *S. hominis* (N=130), *S. lugdunensis* (N=13), *S. saprophyticus* (N=12), and *S. simulans* (N=2).

Abbreviations: AfME, Africa and Middle East; APAC, Asia Pacific; LATAM, Latin America; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; N, total number of isolates; n, number of isolate of a particular phenotype; PRSP, penicillin-resistant *Streptococcus pneumoniae*; PSSP, penicillin-susceptible *Streptococcus pneumoniae*; CoNS, coagulase-negative staphylococci.

Antimicrobial Activity of Ceftaroline and Comparators

S. aureus

Ceftaroline showed potent activity (susceptibility 96.8%, MIC_{90} 1 mg/L) against all isolates of *S. aureus* globally. Among the comparators, all agents except erythromycin and levofloxacin showed good activity (susceptibility 93.4%–100.0%, MIC_{90} 0.12–2 mg/L) against all *S. aureus* isolates. Notably, all the isolates were susceptible to linezolid (MIC_{90} 2 mg/L) and vancomycin (MIC_{90} 1 mg/L; Table 2).

Table 2 Antimicrobial Activity of Ceftaroline and Comparators Against Gram-Positive Isolates from Blood Collected Globally in 2017–2020

Drugs		%S		MIC (mg/L)		
	N	CLSI	EUCAST	MIC_{50}	MIC_{90}	MIC Range
S. aureus						
Ceftaroline	6867	96.8	96.8	0.25	1	0.015–16
Daptomycin	6867	99.8	99.8	0.5	1	0.06–8
Erythromycin	6867	61.1	63.4	0.5	8	0.12–16
Levofloxacin[a]	7373	76.4	76.4	0.25	8	0.03–64
Linezolid	7373	100.0	100.0	2	2	0.5–16
Minocycline	1414	96.4	93.4	0.25	0.5	0.12–16
Tigecycline[b]	7373	99.7	99.7	0.12	0.12	0.015–2
TMP-SMX	6867	98.0	98.0	0.06	0.25	0.03–8
Vancomycin	7373	100.0	100.0	1	1	0.25–2
MRSA						
Ceftaroline	2097	89.8	89.8	0.5	2	0.015–16
Daptomycin	2097	99.5	99.5	0.5	1	0.12–8
Erythromycin	2097	33.6	34.7	8	16	0.12–16
Levofloxacin[a]	2217	37.9	37.9	8	8	0.03–64

(*Continued*)

Table 2 (Continued).

Drugs		%S		MIC (mg/L)		
	N	CLSI	EUCAST	MIC_{50}	MIC_{90}	MIC Range
Linezolid	2217	100.0	100.0	2	2	0.5–4
Minocycline	600	92.8	87.2	0.12	2	0.12–16
Tigecycline[b]	2217	99.0	99.0	0.12	0.25	0.015–2
TMP-SMX	2097	95.6	95.6	0.12	0.5	0.03–8
Vancomycin	2217	100.0	100.0	1	1	0.25–2
MSSA						
Ceftaroline	4685	100.0	100.0	0.25	0.25	0.015–4
Daptomycin	4685	99.9	99.9	0.5	0.5	0.06–8
Erythromycin	4685	73.7	76.6	0.5	8	0.12–16
Levofloxacin[a]	5071	93.1	93.1	0.25	0.5	0.03–64
Linezolid	5071	100.0	100.0	2	2	0.5–16
Minocycline	814	99.0	98.0	0.25	0.25	0.12–16
Tigecycline[b]	5071	99.9	99.9	0.06	0.12	0.015–1
TMP-SMX	4685	99.1	99.1	0.06	0.25	0.03–8
Vancomycin	5071	100.0	100.0	1	1	0.25–2
S. pneumoniae						
Ceftaroline	2445	99.9	99.6	0.008	0.12	0.004–1
Ceftriaxone	2755	96.4	90.3	0.03	0.5	0.015–8
Erythromycin	2751	76.9	76.9	0.03	2	0.008–128
Levofloxacin[a]	2755	99.5	99.5	1	1	0.06–16
Linezolid	2755	100.0	100.0	1	1	0.06–2
Minocycline	801	82.3	77.3	0.25	4	0.015–16
Tigecycline[b]	2755	99.8	NA	0.03	0.03	0.008–0.5
Vancomycin	2755	100.0	100.0	0.25	0.5	0.008–1
S. agalactiae						
Ceftaroline[c]	662	100.0	NA	0.015	0.015	0.004–0.06
Ceftriaxone[c]	801	99.9	NA	0.06	0.12	0.015–1
Daptomycin	28	100.0	100.0	0.25	0.5	0.12–0.5
Erythromycin	662	61.8	61.8	0.06	2	0.015–2
Levofloxacin[a]	801	94.5	94.5	1	2	0.06–64
Linezolid	801	100.0	100.0	1	2	0.5–2
Minocycline	167	24.0	19.8	8	8	0.06–16

(*Continued*)

Table 2 (Continued).

Drugs		%S		MIC (mg/L)		
	N	CLSI	EUCAST	MIC_{50}	MIC_{90}	MIC Range
Tigecycline[b]	801	99.9	99.8	0.03	0.06	0.008–1
Vancomycin	801	100.0	100.0	0.5	0.5	0.03–1
S. dysgalactiae						
Ceftaroline[c]	316	100.0	NA	0.008	0.015	0.004–0.06
Ceftriaxone[c]	316	100.0	NA	0.03	0.06	0.015–0.5
Daptomycin	53	100.0	100.0	0.06	0.25	0.06–0.25
Erythromycin	316	73.4	73.4	0.06	2	0.03–2
Levofloxacin[a]	316	97.2	97.2	0.5	1	0.12–16
Linezolid	316	100.0	100.0	1	2	0.25–2
Minocycline	53	66.0	64.2	0.12	4	0.25–8
Tigecycline[b]	316	99.7	95.9	0.06	0.12	0.015–0.5
Vancomycin	316	100.0	100.0	0.25	0.5	0.015–1
S. pyogenes						
Ceftaroline[c]	690	100.0	NA	0.004	0.008	0.004–0.06
Ceftriaxone[c]	704	100.0	NA	0.03	0.03	0.015–0.12
Daptomycin	146	100.0	100.0	0.06	0.12	0.03–0.5
Erythromycin	690	88.3	88.3	0.03	2	0.015–2
Levofloxacin[a]	704	99.3	99.3	0.5	1	0.12–8
Linezolid	704	100.0	100.0	1	1	0.12–2
Minocycline	160	83.1	78.1	0.06	4	0.03–4
Tigecycline[b]	704	100.0	100.0	0.03	0.06	0.008–0.12
Vancomycin	704	100.0	100.0	0.5	0.5	0.03–1
CoNS[d]						
Amoxy/clav	767	NA	NA	2	16	0.03–16
Ceftaroline	4006	NA	NA	0.5	2	0.015–32
Ceftriaxone	767	NA	NA	16	64	0.03–128
Daptomycin	4006	99.8	99.8	0.5	1	0.06–8
Erythromycin	4006	24.7	24.9	8	16	0.12–16
Levofloxacin[a]	4155	34.9	34.9	4	8	0.015–64
Linezolid	4155	98.7	98.7	1	2	0.5–16
Minocycline	766	99.9	96.7	0.25	0.5	0.12–16
Pip/taz	767	NA	NA	2	32	0.03–32

(*Continued*)

Table 2 (Continued).

Drugs		%S		MIC (mg/L)		
	N	CLSI	EUCAST	MIC_{50}	MIC_{90}	MIC Range
Tigecycline[b]	4154	99.2	99.2	0.12	0.25	0.015–2
TMP-SMX	4006	53.0	53.0	2	4	0.03–8
Vancomycin	4155	100.0	100.0	2	2	0.12–32
Staphylococcus epidermis						
Amoxy/clav	464	NA	NA	2	16	0.03–16
Ceftaroline	2240	NA	NA	0.25	1	0.015–32
Ceftriaxone	464	NA	NA	16	64	0.03–128
Daptomycin	2240	99.8	99.8	0.5	1	0.06–8
Erythromycin	2240	31.7	31.9	8	16	0.12–16
Levofloxacin[a]	2326	42	42	4	8	0.03–64
Linezolid	2326	97.9	97.9	1	2	0.5–16
Minocycline	464	100.0	97.0	0.25	0.5	0.12–4
Pip/taz	464	NA	NA	1	32	0.12–32
Tigecycline[b]	2326	99.4	99.4	0.12	0.25	0.015–2
TMP-SMX	2240	57.1	57.1	2	4	0.03–8
Vancomycin	2326	99.9	99.9	2	2	0.12–32
Staphylococcus haemolyticus						
Amoxy/clav	138	NA	NA	16	16	0.03–16
Ceftaroline	1552	NA	NA	2	2	0.06–8
Ceftriaxone	138	NA	NA	64	128	0.03–128
Daptomycin	1552	99.9	99.9	0.25	0.5	0.06–2
Erythromycin	1552	12.7	12.8	8	8	0.12–16
Levofloxacin[a]	1615	21.6	21.6	8	8	0.03–64
Linezolid	1615	99.8	99.8	1	2	0.5–16
Minocycline	137	100.0	97.8	0.25	0.5	0.12–4
Pip/taz	138	NA	NA	32	32	0.03–32
Tigecycline[b]	1614	98.9	98.9	0.12	0.25	0.015–2
TMP-SMX	1552	45.6	45.6	4	4	0.06–8
Vancomycin	1615	100	100	1	2	0.12–4

Notes: [a]Susceptible, increased exposure for EUCAST breakpoints. [b]Data for tigecycline was interpreted using FDA approved breakpoints. [c]EUCAST has not published breakpoints for ceftaroline, and ceftriaxone tested against β-haemolytic streptococci; EUCAST states that susceptibility to these agents can be inferred from testing benzyl penicillin. [d]Includes isolates of *S. capitis* (N=57), *S. epidermis* (N=2326), *S. haemolyticus* (N=1615), *S. hominis* (N=130), *S. lugdunensis* (N=13), *S. saprophyticus* (N=12), and *S. simulans* (N=2).

Abbreviations: Amoxy/clav, amoxicillin clavulanate; CoNS, coagulase-negative staphylococci; MIC, minimum inhibitory concentration; MIC_{50} minimum inhibitory concentration required to inhibit 50% of the organisms; MIC_{90} minimum inhibitory concentration required to inhibit 90% of the organisms; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; N, total number of isolates; NA, not available; S, susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

For MRSA isolates, ceftaroline showed good activity (susceptibility 89.8%, MIC_{90} 2 mg/L), globally. Among the comparators, all MRSA isolates, globally were susceptible to linezolid (MIC_{90} 2 mg/L) and vancomycin (MIC_{90} 1 mg/L) while daptomycin, tigecycline and TMP-SMX showed potent activity (susceptibility ≥ 95.6%, MIC_{90} ≤ 1 mg/L), and minocycline showed good activity (CLSI/EUCAST, susceptibility 92.8/87.2%, MIC_{90} 2 mg/L; Table 2).

All isolates of MSSA were susceptible to ceftaroline (MIC_{90} 2 mg/L). Among the comparators, all agents except erythromycin showed potent activity (susceptibility ≥ 99.1%, MIC_{90} ≤ 2 mg/L), while levofloxacin showed good activity (susceptibility 93.1%, MIC_{90} 0.5 mg/L; Table 2).

Among the different regions, ceftaroline showed slightly lower activity against all *S. aureus* (susceptibility 94.0%, MIC_{90} 1 mg/L), and MRSA (susceptibility 84.5%, MIC_{90} 2 mg/L) collected in APAC as compared to other regions (Supplementary Tables 2 and 3).

S. pneumoniae

Globally, ceftaroline showed potent activity (CLSI/EUCAST, susceptibility 99.9/99.6%, MIC_{90} 0.12 mg/L) against all isolates of *S. pneumoniae*. Among the comparators, all agents except erythromycin and minocycline showed potent activity (susceptibility ≥ 96.4%, MIC_{90} ≤ 1 mg/L), against all isolates of *S. pneumoniae*. Additionally, all the isolates were susceptible to linezolid (MIC_{90} 1 mg/L) and vancomycin (0.5 mg/L; Table 2).

Against PRSP isolates, ceftaroline showed potent activity (susceptibility 99.2%, MIC_{90} 0.25 mg/L) per CLSI and good activity (susceptibility 91.4%, MIC_{90} 0.25 mg/L) per EUCAST. Among the comparators, levofloxacin, linezolid, tigecycline, and vancomycin showed potent activity (susceptibility ≥ 95.5%, MIC_{90} ≤ 2 mg/L) against PRSP isolates, with all isolates being susceptible to linezolid and vancomycin (Table 3).

All isolates of PSSP were susceptible to ceftaroline (MIC_{90} 0.015 mg/L). Among comparator agents, all PSSP isolates were susceptible to ceftriaxone (MIC_{90} 0.015 mg/L), linezolid (MIC_{90} 1 mg/L), tigecycline (MIC_{90} 0.03 mg/L), and vancomycin (MIC_{90} 0.25 mg/L), while levofloxacin showed potent activity (susceptibility 99.9%, MIC_{90} 1 mg/L, Table 3).

Among the different regions, per EUCAST, ceftaroline showed lower activity against PRSP isolates collected in AfME (susceptibility 81.8%, MIC_{90} 0.5 mg/L), Europe (susceptibility 88.6%, MIC_{90} 0.5 mg/L), and APAC (susceptibility 91.7%, MIC_{90} 0.25 mg/L) as compared to LATAM and North America (susceptibility 100%, MIC_{90} 0.25 mg/L, Supplementary Table 4).

Table 3 Antimicrobial Activity of Ceftaroline and Comparators Against PRSP and PSSP Isolates from Blood Collected Globally in 2017–2020

	CLSI					EUCAST				
	N	%S	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	N	%S	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)
PRSP										
Ceftaroline	246	99.2	0.12	0.25	0.03–1	104	91.4	0.25	0.25	0.06–1
Ceftriaxone	273	65.9	1	2	0.03–8	112	5.4	2	4	0.03–8
Erythromycin	273	18.7	2	2	0.015–128	112	17.0	2	2	0.015–128
Levofloxacin[a]	273	97.1	1	2	0.25–16	112	95.5	1	2	0.25–16
Linezolid	273	100.0	1	1	0.12–2	112	100.0	0.5	1	0.12–2
Minocycline	80	42.5	4	4	0.06–16	23	34.8	4	4	0.06–16
Tigecycline[b]	273	98.5	0.03	0.03	0.008–0.5	112	NA	0.03	0.03	0.008–0.06
Vancomycin	273	100.0	0.5	0.5	0.12–1	112	100.0	0.5	0.5	0.25–1

(*Continued*)

Table 3 (Continued).

	CLSI					EUCAST				
	N	%S	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	N	%S	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)
PSSP										
Ceftaroline	1876	100.0	0.008	0.015	0.004–0.25	1876	100.0	0.008	0.015	0.004–0.25
Ceftriaxone	2097	100.0	0.03	0.06	0.015–1	2097	99.9	0.03	0.06	0.015–1
Erythromycin	2094	89.2	0.03	2	0.008–128	2094	89.2	0.03	2	0.008–128
Levofloxacin[a]	2097	99.9	1	1	0.06–8	2097	99.9	1	1	0.06–8
Linezolid	2097	100.0	1	1	0.06–2	2097	100.0	1	1	0.06–2
Minocycline	593	91.7	0.06	1	0.015–8	593	86.7	0.06	1	0.015–8
Tigecycline[b]	2097	100.0	0.03	0.03	0.008–0.5	2097	NA	0.03	0.03	0.008–0.5
Vancomycin	2097	100.0	0.25	0.5	0.008–1	2097	100.0	0.25	0.5	0.008–1

Notes: [a]Susceptible, increased exposure for EUCAST breakpoints. [b]Data for tigecycline was interpreted using FDA approved breakpoint.
Abbreviations: MIC, minimum inhibitory concentration; MIC_{50} minimum inhibitory concentration required to inhibit 50% of the organisms; MIC_{90} minimum inhibitory concentration required to inhibit 90% of the organisms; N, total number of isolates; PRSP, penicillin-resistant *Streptococcus pneumoniae*; PSSP, penicillin-susceptible *Streptococcus pneumoniae*.

β-Hemolytic Streptococci

Globally, all isolates of *S. agalactiae, S. dysgalactiae*, and *S. pyogenes* were susceptible to ceftaroline ($MIC_{90} \leq$ 0.015 mg/L). Among comparator agents, all isolates of β-hemolytic streptococci were susceptible to daptomycin ($MIC_{90} \leq 0.5$ mg/L), linezolid ($MIC_{90} \leq 1$ mg/L), and vancomycin (MIC_{90} 0.5 mg/L). Against ceftriaxone, all isolates of *S. dysgalactiae* (MIC_{90} 0.06), and *S. pyogenes* (MIC_{90} 0.03 mg/L) were susceptible, while isolates of *S. agalactiae* showed a susceptibility of 99.9% (800/801) with only one isolate being intermediate. Tigecycline showed potent activity (susceptibility ≥99.7%, MIC_{90} 0.06–0.12 mg/L) against isolates of β-hemolytic streptococci with all isolates of *S. pyogenes* being susceptible (Table 2).

CoNS

Ceftaroline showed good activity (MIC_{90} 2 mg/L) against all isolates of CoNS, globally. Among comparator agents, daptomycin, linezolid, minocycline, tigecycline, and vancomycin showed potent activity (susceptibility ≥ 96.7%, MIC_{90} 0.25–2 mg/L) against isolates of CoNS (Table 2).

Against *S. epidermis*, ceftaroline showed a higher activity (MIC_{90} 1 mg/L) than against *S. haemolyticus* (MIC_{90} 2 mg/L). Among the comparator agents, all isolates of *S. haemolyticus* were susceptible to vancomycin (MIC_{90} 2 mg/L). Among the other comparator agents, daptomycin, minocycline, linezolid, tigecycline, and vancomycin (*S. epidermis*) showed potent activity (susceptibility ≥96.7%, MIC_{90} 0.25–2 mg/L) against *S. epidermis* and *S. haemolyticus* isolates collected globally (Table 2).

Among the different geographical regions, ceftaroline showed sustained activity (MIC_{90} 0.5–1 mg/L) across regions against *S. epidermis* isolates. Notably, a lower activity for ceftaroline was observed against *S. haemolyticus* isolates collected in APAC (MIC_{90} 4 mg/L) compared to other regions (MIC_{90} 2 mg/L; Supplementary Tables 2 and 3).

Discussion

The current study assessed the antimicrobial activity of ceftaroline and a panel of comparator agents against isolates of Gram-positive bacteria, including *S. aureus, S. pneumoniae, S. agalactiae, S. dysgalactiae, S. pyogenes*, and CoNS from blood collected globally and across different regions from 2017 to 2020. Overall, ceftaroline showed good activity with susceptibility ≥91.4% (for isolates in which breakpoints for ceftaroline are defined) and an MIC range of 0.004–16 mg/L

against all Gram-positive isolates tested, except MRSA (susceptibility 89.8%, MIC_{90} 2 mg/L). For MRSA, 4 isolates demonstrated MICs above the PK/PD breakpoints for ceftaroline of 8 mg/L (1 isolate from China and 2 isolates from Thailand showing an MIC and 1 isolate from South Korea showing an MIC of 16 mg/L; data not shown). Similarly, 5 isolates of *S. haemolyticus* (4 isolates from China and 1 isolate from Nigeria showing an MIC of 8 mg/L) and 1 isolate of *S. epidermis* (from Brazil showing an MIC of 32 mg/L) demonstrated MICs above the PK/PD breakpoints for ceftaroline (no data shown). Among the comparator agents, all isolates tested were susceptible to vancomycin and linezolid, except for linezolid activity against CoNS (susceptibility 98.7%, MIC_{90} 2 mg/L). Among other agents, daptomycin, and tigecycline showed potent activity (susceptibility ≥ 99.1%, MIC_{90} 0.03–0.25 mg/L) against all isolates tested.

In the current study, ceftaroline showed potent activity (susceptibility 96.8%, MIC_{90} 1mg/L) against all *S. aureus* isolates collected globally. Two previous SENTRY studies assessing ceftaroline activity against Gram-positive isolates from BSI also reported similar findings against *S. aureus*, a 20-year study from 1997 to 2016 (susceptibility 96.2%, MIC_{90} 1 mg/L) and a 10-year study from 2010 to 2019 (susceptibility 96.0%, MIC_{90} 1 mg/L).[5,16] Among the different regions in the current study, ceftaroline showed consistent activity (susceptibility 96.2%–98.4%, MIC_{90} 1mg/L) against all *S. aureus* isolates in all the regions, except APAC, where it was slightly lower (susceptibility 94.0%, MIC_{90} 1mg/L). The previously 10-year SENTRY study (2010–2019) also reported a lower susceptibility for ceftaroline in LATAM-APAC as compared to other regions (LATAM-APAC vs other regions, 91.1% vs 95.4%–98.1%).[16] A similar trend of lower *S. aureus* susceptibility to ceftaroline in APAC (APAC vs other regions, 85.0% vs 91.3%–99.7%) was reported by a previous ATLAS study that assessed in vitro activity of ceftaroline against *S. aureus* isolates collected from various sources, including BSI from 2012 to 2017.[24]

All isolates of MSSA in the current study showed 100% susceptibility to ceftaroline (MIC_{90} 0.25 mg/L). This observation is in line with the previous 10-year SENTRY study (2010–2019) and the ATLAS study (2012–2017; susceptibility > 99.9%, MIC_{90} 0.25 mg/L in both studies).[16,24] However, ceftaroline activity in the current study was lower (susceptibility 89.8%, MIC_{90} 2 mg/L) against MRSA isolates as compared to the overall activity against *S. aureus* and MSSA. Among different regions, the activity of ceftaroline against MRSA in this study was lower in APAC as compared to other regions (susceptibility 84.5%, MIC_{90} 2 mg/L vs susceptibility ≥87.6%, MIC_{90} 1–2 mg/L). These observations are in line with that reported in the previous studies - 10-year SENTRY study (2010–2019) reporting a higher overall MIC_{90} of 2 mg/L for ceftaroline against MRSA compared to 0.25 mg/L against MSSA,[16] and the ATLAS study (2012–2017) reporting an overall susceptibility of 89.3% and an MIC_{90} of 2 mg/L for MRSA and a lower susceptibility of 75.9% in APAC to ceftaroline as compared to the other regions (≥84.4%).[24] Among the comparators, all agents except erythromycin and levofloxacin showed good activity (susceptibility ≥93.4%, MIC_{90} 0.12–2 mg/L) against all *S. aureus* isolates. This data is in line with the previous studies, the 10-year SENTRY study (2010–2019) and the ATLAS study (2012–2017).[16,24] While ceftaroline is active against *S. aureus*, there was lower activity against MRSA and against all isolates in APAC; this needs further surveillance for appropriate treatment and management of *S. aureus* infections.

In the current study, globally, ceftaroline showed potent activity against all isolates of *S. pneumoniae*, (CLSI/EUCAST, susceptibility 99.9%/99.6%, MIC_{90} 0.12 mg/L). A previous study assessing the activity of ceftaroline and its comparators against *S. pneumoniae* isolates from CAP collected in Europe, Asia, and LATAM from 2015 to 2017 also reported potent activity of ceftaroline against all *S. pneumoniae* (CLSI, susceptibility 99.9%, MIC_{90} 0.12 mg/L) isolates.[25] Globally, all isolates of PSSP in the current study were susceptible to ceftaroline (MIC_{90} 0.015 mg/L). However, for PRSP isolates, while ceftaroline demonstrated potent activity per CLSI (susceptibility 99.2%, MIC_{90} 0.25 mg/L), the activity was lower per EUCAST (susceptibility 91.4%, MIC_{90} 0.25 mg/L). Across the different regions, ceftaroline activity was sustained per CLSI (susceptibility ≥98.4%, MIC_{90} 0.25 mg/L). However, per EUCAST, while all PRSP isolates in LATAM and North America were susceptible to ceftaroline (MIC_{90} 0.25), lower activity was observed in APAC (susceptibility 91.7%, MIC_{90} 0.25 mg/L), Europe (susceptibility 88.6%, MIC_{90} 0.5 mg/L), and AfME (susceptibility 81.8%, MIC_{90} 0.5 mg/L). Interestingly, a previous AWARE study that assessed activity of ceftaroline against *S. pneumoniae* isolates (per EUCAST) from CAP collected in AfME, Asia, Europe, Oceania, and LATAM from 2015 to 2016 reported 100% susceptibility for PRSP isolates collected in LATAM and Oceania (MIC_{90} 0.25 mg/L) and potent but comparatively lower activity in Europe (susceptibility 94.6%, MIC_{90} 0.25 mg/L) and further lower activity in AfME (susceptibility 86.8%, MIC_{90} 0.5 mg/L) and Asia (susceptibility 77.4%, MIC_{90} 1 mg/L).[26] Among the

comparators, all agents except ceftriaxone, erythromycin, and minocycline demonstrated potent activity (susceptibility ≥ 96.4%, MIC_{90} 0.03–1 mg/L) against all PRSP isolates, globally.

In our study, all isolates of β-hemolytic streptococci globally were susceptible to ceftaroline (*S. agalactiae* and *S. dysgalactiae*: MIC_{90} 0.015 mg/L; *S. pyogenes*: MIC_{90} 0.008 mg/L). These data are in line with a previous ATLAS study that assessed activity of ceftaroline and its comparators against isolates from SSTI collected in AfME, APAC, Europe, and LATAM from 2015 to 2017 (*S. agalactiae*: MIC_{90} 0.015–0.03 mg/L; *S. dysgalactiae*: MIC_{90} 0.008–0.015 mg/L; *S. pyogenes*: MIC_{90} 0.008 mg/L).[27]

Against CoNS isolates, ceftaroline had an MIC_{90} of 2 mg/L, globally in this study. A previous AWARE study that evaluated the activity of ceftaroline against CoNS collected from various sources in the US from 2013 to 2014 reported an MIC_{90} of 0.5 mg/L against isolates from BSIs.[17] However, ceftaroline had an MIC_{90} of 0.5 mg/L against *S. epidermis* and 2 mg/L against isolates of *S. haemolyticus* collected in North America, which is in line with the previous AWARE study conducted in the US.[17]

This study has certain limitations. A pre-defined number of isolates were collected each year from the centers, and hence, the results of the study cannot be interpreted as prevalence of infection or used for general epidemiological assessment. Clinical and epidemiological information about the patient population were not available for the isolates collected in this study. Information such as the infection source, type, and history antimicrobial use could add value and insight to the interpretation of the susceptibility results. Not all antimicrobials were tested every year and the number of participating centers in each region varied between the years.

Conclusions

Overall, ceftaroline showed good in vitro activity against global isolates of Gram-positive bacteria, including *S. aureus, S. pneumoniae, S. pyogenes, S. agalactiae, S. dysgalactiae*, and CoNS, tested in this study (2017–2020). Among the comparators, linezolid, vancomycin, daptomycin, and tigecycline showed potent activity against all isolates. In the recent years, with increase in use of antimicrobials and spread of drug resistance among Gram-positive bacteria, it has become challenging to manage the treatment of drug-resistant BSIs, especially those caused by *S. aureus* and, particularly, MRSA, where the mortality rates are high. Hence, monitoring and surveillance of global as well as regional longitudinal trends of resistance rates among Gram-positive isolates causing BSIs are important to limit the spread of AMR and establish appropriate stewardship measures. Despite the study limitations, data presented in the study provide crucial insights into the in vitro activity of ceftaroline, which may be considered as a good treatment option for BSIs caused by these Gram-positive organisms.

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