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Antimicrobial Susceptibility Studies

Update on the *in vitro* activity of ceftaroline against *Staphylococcus aureus* from United States (US) medical centers stratified by infection type (2018–2020)

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ABSTRACT

Ceftaroline and comparators were tested against 9,268 *Staphylococcus aureus* isolates from 33 United States hospitals (2018–2020). Ceftaroline ($MIC_{50/90}$, 0.25/1 mg/L) susceptibility ranged from 95.4% (pneumonia) to 98.5% (skin and skin structure) and was 97.2% overall. Ceftaroline retained potent and broad-spectrum activity against methicillin-resistant isolates, with a 93.4% overall susceptibility.

Ceftaroline is an advanced-generation cephalosporin active against methicillin-susceptible (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftaroline fosamil (Teflaro®), the prodrug of ceftaroline, was approved in October 2010 by the United States Food and Drug Administration (US FDA) for the treatment of adults with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSI). In 2015, the US FDA approved a label expansion to include clinical data from patients with *S. aureus* bacteremia. In 2016, ceftaroline fosamil was approved for pediatric use with the same indications [1–3]. Moreover, ceftaroline has also been used off-label to treat various other infection types [1,2].

The antimicrobial resistance surveillance program, Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE), was designed to monitor the activity of ceftaroline and comparator agents as well as provide contemporary and longitudinal information on the activity of this agent against relevant pathogens. Previous reports from the AWARE program have provided analyses of ceftaroline activity against bacterial isolates recovered from indicated infection sites, specific patient populations, and selected organism groups and resistant subsets, as well as yearly variation on its *in vitro* activity and potency [4–6]. In this investigation, we evaluated the *in vitro* activity of ceftaroline against contemporary (2018-2020) *S. aureus* isolates from US medical centers stratified by infection type.

Clinically significant bacterial isolates were consecutively collected (1/patient) from various infection types. All *S. aureus* isolates (n = 9,268) were from patients hospitalized in medical centers that participated in the AWARE Program. Isolates were from 33 medical centers (30-31 centers per year) located in 23 states from all 9 Census Divisions. Isolates were collected from patients with SSSI (n = 4,343; 46.9%), pneumonia (n = 2,260; 24.4%), bloodstream infection (BSI; n = 2,235; 24.1%), and other infections (n=430; 4.6%).

Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standard Institute (CLSI) [7], and susceptibility interpretations were based on CLSI (M100-S32) and US FDA breakpoint criteria [8–10]. A susceptible breakpoint of ≤1 mg/L was applied for ceftaroline as indicated by CLSI and EUCAST and based on ceftaroline fosamil 600 mg q12h dosage [8,11]. Results were stratified by infection type and resistance profile [8–10].

Organisms were tested in cation-adjusted Mueller-Hinton broth (Thermo Fisher Scientific, Waltham, Massachusetts, USA). MIC panels were manufactured at JMI Laboratories (North Liberty, Iowa, USA) and frozen at -80°C until used. Ceftaroline and comparator agents were tested simultaneously using the same bacterial inoculum and testing reagents. Concurrent testing of quality control (QC) strains assured proper test conditions. All QC results were within CLSI published ranges [8].

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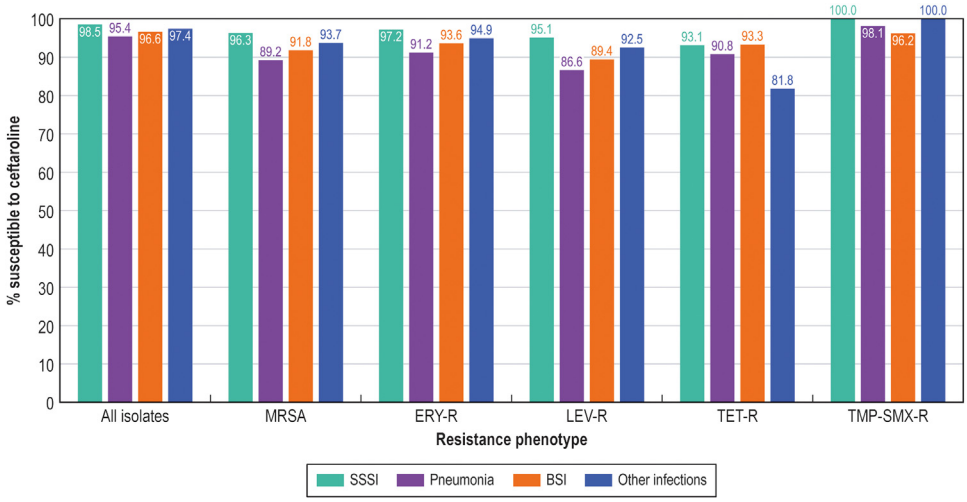

Fig. 1. Antimicrobial activity of ceftaroline against *S. aureus* from US medical centers stratified by resistance phenotype and infection type (2018–2020).

Ceftaroline was active against 97.2% of *S. aureus* isolates ($MIC_{50/90}$, 0.25/1 mg/L), with susceptibility rates ranging from 95.4% (pneumonia) to 98.5% (SSSI; Tables 1 and S1 and Fig. 1). Ceftaroline was highly active against MSSA isolates ($MIC_{50/90}$, 0.25/0.25 mg/L; 100.0% susceptible) and retained potent activity and broad spectrum against MRSA (41.9% of isolates; $MIC_{50/90}$, 1/1 mg/L), with susceptibility rates varying from 96.3% (SSSI) to 89.2% (pneumonia). Susceptibility of MRSA was 93.4% overall (Tables 1 and S1 and Fig. 1). Moreover, all ceftaroline-nonsusceptible isolates exhibited a ceftaroline MIC of 2 mg/L (n = 258; Table S1), which is considered susceptible dose-dependent by CLSI (based on 600 mg q8 hours as a 2-hour infusion), intermediate by EUCAST (indications other than pneumonia [EUCAST 2022]), and the US FDA (i.e., 0.0% resistance; Table 1). The percentage of isolates with ceftaroline MICs of 2 mg/L varied slightly but did not show any trends during the study period (Table S1).

Overall susceptibility rates to erythromycin, levofloxacin, tetracycline, and trimethoprim-sulfamethoxazole (TMP-SMX) were 44.0%, 67.9%, 94.1%, and 97.5%, respectively (Table 1). Ceftaroline retained good activity against *S. aureus* resistant to erythromycin (n = 4,784; $MIC_{50/90}$, 0.5/1 mg/L; 94.8% susceptible), levofloxacin (n = 2,944; $MIC_{50/90}$, 1/1 mg/L; 91.4% susceptible), tetracycline (n = 453; $MIC_{50/90}$, 0.5/1 mg/L; 92.3% susceptible), and/or TMP-SMX (n = 228; $MIC_{50/90}$, 0.5/1 mg/L; 98.7% susceptible; Fig. 1). Among the resistant subsets, ceftaroline susceptibility rates were generally highest among isolates from SSSI (ranging from 93.1% [tetracycline-resistant subset] to 100.0% [TMP-SMX-resistant subset]), followed by other infections (81.8% [tetracycline-resistant subset] to 100.0% [TMP-SMX-resistant subset]), BSI (89.4% [levofloxacin-resistant subset] to 96.2% [TMP-SMX-resistant subset]), and pneumonia (86.6% [levofloxacin-resistant subset] to 98.1% [TMP-SMX-resistant subset]; Fig. 1).

Dalbavancin ($MIC_{50/90}$, 0.03/0.03 mg/L) and vancomycin ($MIC_{50/90}$, 1/1 mg/L) exhibited complete activity (100.0% susceptible), whereas daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and linezolid ($MIC_{50/90}$, 1/2 mg/L) were active against ≥99.8% of isolates (Table 1).

The results of our investigation corroborate and expand data previously published by our group and other investigators by demonstrating that ceftaroline remained highly active against *S. aureus* isolates causing infection in US medical centers [2,4-6,11]. Furthermore, all ceftaroline-nonsusceptible MRSA isolates displayed a ceftaroline MIC value of 2 mg/L and were categorized as susceptible dose-dependent or intermediate [8–10].

Other antimicrobial agents used to treat *S. aureus* infections, such as dalbavancin, daptomycin, linezolid, and vancomycin also showed excellent coverage against the contemporary *S. aureus* collection evaluated in this investigation, with susceptibility rates of 99.8% to 100.0%. Vancomycin is often used as an initial therapy to treat MRSA infections; however, while high exposure (AUC_{24}/MIC ≥350 or 400) may be necessary to achieve a successful clinical response, high serum trough concentrations (>20 mg/L) are associated with a greater risk of nephrotoxicity [12]. Moreover, it has been shown that it is practically impossible to achieve a high probability of target attainment (PTA) for vancomycin above MIC values of 1 mg/L without substantially increasing the risk of nephrotoxicity [13].

Linezolid and daptomycin have been used as alternatives to vancomycin to treat Gram-positive bacterial infections, particularly those caused by MRSA. However, more recent studies have shown that these antibiotics may be under-dosed at the standard regimens to achieve bacteriostatic or bactericidal pharmacokinetic/pharmacodynamic (PK/PD) targets against contemporary *S. aureus* isolates. Cristinacce and colleagues [14] have shown that increasing the dose of vancomycin and daptomycin improved PTAs and weighted PK/PD target attainment values but did not lead to PTAs >90% at the respective MIC_{90} values, even at the highest doses and lowest exposure targets. In these cases, the potential side effects of a dose increase beyond the label recommendation requires careful evaluation [14]. In contrast, the standard labeled dose of ceftaroline fosamil for adults with SSSI (600 mg q12h) achieves PTAs values at or close to 100% against *S. aureus* isolates with ceftaroline MICs ≤2 mg/L. Moreover, >90% PTA was predicted for the ceftaroline fosamil 600mg q8h dosage regimen against *S. aureus* with ceftaroline MICs ≤4 mg/L [14,15].

In conclusion, the results of this comprehensive surveillance investigation indicate that ceftaroline represents a valuable treatment option for US *S. aureus* infections. Even the small percentage of infections caused by isolates with ceftaroline MIC of 4 mg/L can potentially be treated with the high ceftaroline dosing regimen (600 mg every 8 hour with 2-hour infusion) [15].

Table 1
Antimicrobial activity of ceftaroline and comparator agents against *S. aureus* from US medical centers.

Organism/antimicrobial (no. tested)	All isolates					% Susceptible per CLSI (no. of isolates)			
	MIC_{50} [a]	MIC_{90} [a]	MIC range	%S[a]	%R	SSSI	Pneumonia	BSI	Other
S. aureus (9,268)						(4,343)	(2,260)	(2,235)	(430)
Ceftaroline	0.25	1	≤0.06 to 2	97.2	0.0	98.5	95.4	96.6	97.4
Oxacillin	0.5	>2	≤0.06 to >2	58.1	41.9	57.8	57.6	58.7	59.3
Clindamycin	0.06	>2	≤0.03 to >2	86.4	13.4	88.6	83.3	85.5	84.7
Dalbavancin	0.03	0.03	≤0.002 to 0.25	100.0		100.0	100.0	100.0	100.0
Daptomycin	0.25	0.5	≤0.12 to 2	>99.9		100.0	>99.9	>99.9	99.8
Erythromycin	8	>8	≤0.06 to >8	44.0	51.6	44.5	43.3	43.8	44.4
Levofloxacin	0.25	>4	0.06 to >4	67.9	31.8	69.5	65.8	67.6	65.6
Linezolid	1	2	≤0.12 to >8	>99.9	<0.1	>99.9	100.0	100.0	100.0
Tetracycline	≤0.5	1	≤0.5 to >8	94.1	4.9	93.4	94.1	95.1	96.3
TMP-SMX	≤0.5	≤0.5	≤0.5 to >16	97.5	2.5	97.4	97.7	97.7	97.0
Vancomycin	1	1	≤0.12 to 2	100.0	0.0	100.0	100.0	100.0	100.0
MSSA (5,381)						(2,512)	(1,301)	(1,313)	(255)
Ceftaroline	0.25	0.25	≤0.06 to 0.5	100.0	0.0	100.0	100.0	100.0	100.0
Oxacillin	0.5	1	≤0.06 to 2	100.0	0.0	100.0	100.0	100.0	100.0
Clindamycin	0.06	0.12	≤0.03 to >2	95.8	4.2	95.9	95.6	95.6	96.1
Dalbavancin	0.03	0.03	≤0.002 to 0.12	100.0		100.0	100.0	100.0	100.0
Daptomycin	0.25	0.5	≤0.12 to 2	>99.9		100.0	100.0	99.9	100.0
Erythromycin	0.25	>8	≤0.06 to >8	65.6	28.9	65.8	65.0	65.8	65.5
Levofloxacin	0.25	1	0.06 to >4	91.2	8.6	91.2	92.2	91.2	86.7
Linezolid	1	2	≤0.12 to 4	100.0	0.0	100.0	100.0	100.0	100.0
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	95.8	3.2	94.9	96.0	96.8	97.3
TMP-SMX	≤0.5	≤0.5	≤0.5 to >16	99.4	0.6	99.4	99.5	99.5	99.2
Vancomycin	1	1	≤0.12 to 2	100.0	0.0	100.0	100.0	100.0	100.0
MRSA (3,887)						(1,831)	(959)	(922)	(175)
Ceftaroline	1	1	0.12 to 2	93.4	0.0	96.3	89.2	91.8	93.7
Oxacillin	>2	>2	>2 to >2	0.0	100.0	0.0	0.0	0.0	0.0
Clindamycin	0.06	>2	≤0.03 to >2	73.4	26.3	78.5	66.6	71.3	68.0
Dalbavancin	0.03	0.03	≤0.002 to 0.25	100.0		100.0	100.0	100.0	100.0
Daptomycin	0.25	0.5	≤0.12 to 2	99.9		100.0	99.9	100.0	99.4
Erythromycin	>8	>8	≤0.06 to >8	14.2	83.0	15.2	13.8	12.7	13.7
Levofloxacin	4	>4	0.06 to >4	35.7	63.9	39.6	30.1	33.8	34.9
Linezolid	1	2	≤0.12 to >8	>99.9	<0.1	99.9	100.0	100.0	100.0
Tetracycline	≤0.5	2	≤0.5 to >8	91.8	7.2	91.2	91.5	92.7	94.9
TMP-SMX	≤0.5	≤0.5	≤0.5 to >16	94.9	5.1	94.7	95.3	95.1	93.7
Vancomycin	1	1	0.25 to 2	100.0	0.0	100.0	100.0	100.0	100.0

BSI = bloodstream infection; MRSA = methicillin-resistant *S. aureus*; SSSI = skin and skin structure infection; TMP-SMX = trimethoprim-sulfamethoxazole.
[a] MIC_{50}, MIC_{90}, and susceptibility rate (CLSI) for the isolate collection combined.

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JMI Laboratories contracted to perform services in 2021 for AbbVie Inc., Affinity Biosensors, AimMax Therapeutics, Inc., Alterity Therapeutics, Amicrobe, Inc., Arietis Pharma, Armata Pharmaceuticals, Inc., Astrellas Pharma Inc., Basilea Pharmaceutica AG, Becton, Dickinson and Company (BD), bioMérieux, Inc., Boost Biomes, Brass Dome Ventures Ltd., Bravos Biosciences, Bugworks Research Inc., Centers for Disease Control and Prevention, Cerba Research, Cidara Therapeutics, Cipla Ltd., ContraFect Corp., CXC7, DiamondV, Enveda Biosciences, Fedora Pharmaceuticals, Inc., Fimbrion Therapeutics, First Light Diagnostics, Forge Therapeutics, Inc., Fox Chase Cancer Center, GlaxoSmithKline plc (GSK), Harvard University, Institute for Clinical Pharmacodynamics (ICPD), International Health Management Associates (IHMA), Inc., Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences, Inc., Laboratory Specialists, Inc. (LSI), Meiji Seika Pharma Co., Ltd., Melinta Therapeutics, Menarini Group, Merck & Co., Inc., MicuRx Pharmaceuticals Inc., Mutabilis, Nabriva Therapeutics, National Institutes of Health, Novome Biotechnologies, Omnix Medical Ltd., Paratek Pharma, Pattern Bioscience, Pfizer Inc., Prokaryotics Inc., Pulmocide Ltd., QPEX Biopharma, Inc., Roche Holding AG, Roivant Sciences, SeLux Diagnostics, Inc., Shionogi Inc., Sinovent Pharmaceuticals, Inc., SNIPR Biome ApS, Spero Therapeutics, Summit Therapeutics, Inc., T2 Biosystems, TenNor Therapeutics, Thermo Fisher Scientific, University of Southern California, University of Wisconsin, USCAST, U.S. Food and Drug Administration, Venatorx Pharmaceutics, Inc., Weill Cornell Medicine, and Wockhardt Ltd. There are no speakers' bureaus or stock options to declare.

Authors' contributions

Helio S. Sader: Conceptualization, Formal analysis, Data curation, Writing – original draft, Visualization, Funding acquisition. Mariana Castanheira: Conceptualization, Validation, Resources, Writing – review & editing, Visualization, Supervision, Funding acquisition. Leonard R. Duncan: Methodology, Formal analysis, Investigation, Data curation, Project administration. Rodrigo E. Mendes: Methodology, Formal analysis, Investigation, Data curation, Writing – review & editing, Software, Validation, Supervision.

Author Statement

The content has been read and approved by all co-authors and the manuscript has not been submitted elsewhere. Furthermore, all authors agree to transfer the copyright, following the policies of the journal at the time of acceptance/publication.

Ethical Approval

Not required.

Supplementary materials

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