Ceftaroline Activity against *Staphylococcus aureus* Isolated from Patients with Infective Endocarditis Worldwide (2010–2019)

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INTRODUCTION

- *Streptococcus viridans* initially was reported as the most common cause of IE; however, *Staphylococcus aureus*, which is most often associated with invasive procedures and health care contact, has overtaken streptococci as the most common cause of IE.
- Prosthetic valve IE and staphylococcal IE are associated with an increased risk of in-hospital death, while viridans streptococcal IE are associated with a decreased risk.
- Ceftaroline fosamil is an advanced-generation cephalosporin active against methicillin-susceptible (MSSA) and methicillin-resistant *S. aureus* (MRSA).
- Ceftaroline was approved by the US FDA for the treatment of adults with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSI) in October 2010; in 2015, the US FDA approved a label expansion to include clinical data from patients with *S. aureus* bacteremia.
- Moreover, many reports have shown that ceftaroline is effective in treating patients with bloodstream infections (BSI) and IE.
- We evaluated the *in vitro* activity of ceftaroline against a large collection of *S. aureus* recovered from patients hospitalized with IE worldwide. We also compared the antimicrobial susceptibility of the *S. aureus* from IE with the entire collection of *S. aureus* from BSI.

MATERIALS AND METHODS

- The SENTRY Antimicrobial Surveillance Program collected 23,833 *S. aureus* isolates from patients with bloodstream infections in medical centers located in:
  - North America: 11,900 isolates from 176 medical centers in the US and Canada.
  - Europe: 7,772 isolates from 83 centers in 24 countries.
  - Latin America and the Asia-Pacific region (LATAM-APAC): 4,161 isolates from 81 medical centers in 26 countries.
- Among those 23,833 isolates, 396 were recovered from patients with a diagnosis of IE, including:
  - 124 isolates from North America (19 US medical centers).
  - 213 isolates from Europe (34 medical centers in 16 countries).
  - 59 isolates from LATAM-APAC (22 centers in 11 countries).
- The isolates (1/infection episode) were collected consecutively between January 2010 and December 2019.
- Isolates were determined to be clinically significant based on local guidelines and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) along with limited demographic information, which included the source of BSI.
- Isolates were susceptibility tested by broth microdilution at JMI Laboratories following guidelines in the CLSI M07 and by using reference 96-well panels manufactured by JMI Laboratories (2015–19) or acquired from Thermo Fisher (Cleveland, Ohio, USA; 2010–14).

RESULTS

- Ceftaroline was active against 95.2% of IE isolates ($MIC_{50/90}$, 0.25/1 mg/L; Table 1).
- Ceftaroline susceptibility was higher in North America ($MIC_{50/90}$, 0.25/1 mg/L; 99.2% susceptible) and LATAM-APAC ($MIC_{50/90}$, 0.25/0.5 mg/L; 98.3% susceptible) than in Europe ($MIC_{50/90}$, 0.25/1 mg/L; 92.0% susceptible; Table 1).
- The overall oxacillin resistance (MRSA) rate among IE isolates was 29.0%, and MRSA rate was higher in North America (40.3%) than in Europe (25.4%) and LATAM-APAC (18.6%; Table 1).
- All ceftaroline nonsusceptible MRSA isolates from patients with IE (n=19) had a ceftaroline MIC of 2 mg/L (intermediate [US FDA] or susceptible dose-dependent [CLSI]; Figure 1).
- The highest ceftaroline MIC value among MSSA isolates from IE was 0.5 mg/L (n=281; $MIC_{50/90}$, 0.25/0.25 mg/L; 100.0% susceptible).
- Among MRSA isolates from IE, ceftaroline MIC values were lower in North America (n=50; $MIC_{50/90}$, 0.5/1 mg/L; 98.0% susceptible [Figure 1]) and LATAM-APAC (n=11; $MIC_{50/90}$, 0.5/1 mg/L; 90.9% susceptible) compared to Europe (n=54; $MIC_{50/90}$, 1/2 mg/L; 68.5% susceptible; Table 1).
- Dalbavancin ($MIC_{50/90}$, ≤0.03/0.06 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), linezolid ($MIC_{50/90}$, 1/2 mg/L), teicoplanin ($MIC_{50/90}$, ≤2/≤2 mg/L), and vancomycin ($MIC_{50/90}$, 1/1 mg/L) exhibited complete activity (100.0% susceptible) against *S. aureus* from IE (Table 1).
- Isolates from all BSI combined (n=23,833; $MIC_{50/90}$, 0.25/1 mg/L; 96.0% susceptible) exhibited ceftaroline susceptibility similar to isolates from IE (Table 1 and Figure 2 [North America]).
- All MSSA isolates from BSI (n=15,188; $MIC_{50/90}$, 0.25/0.25 mg/L) were susceptible to ceftaroline; whereas among MRSA, ceferoline susceptibility rates were 95.6% in North America ($MIC_{50/90}$, 0.5/1 mg/L [Figure 2]), 82.2% in Europe ($MIC_{50/90}$, 1/2 mg/L), and 74.9% in LATAM-APAC ($MIC_{50/90}$, 1/2 mg/L; Table 1).
- Only 20 of 23,833 BSI isolates (<0.1%) exhibited ceftaroline MICs >2 mg/L, 15 isolates had ceftaroline MICs of 4 mg/L (1 from the US, 3 from Italy, and 11 from LATAM-APAC, including Hong Kong [1], Japan [2], Peru [2], South Korea [4], and Thailand [2]), and 5 isolates displayed ceftaroline MICs of 8 mg/L (1 from Spain, 1 from South Korea, and 3 from Thailand; data not shown).
- Although susceptibility to ceftaroline among IE isolates was higher in North America (99.2%) compared to Europe (92.0%) and LATAM-APAC (98.3%), susceptibility to other drugs such as oxacillin, clindamycin, erythromycin, and levofloxacin were lower in North America compared to Europe and LATAM-APAC (Table 1).
- Ceftaroline and oxacillin susceptibility rates among BSI isolates from North America oscillated with no significant yearly changes or clear trend during the 10-year study period (Table 2 and Figure 3).

CONCLUSIONS

- Ceftaroline demonstrated potent *in vitro* activity against a large collection of *S. aureus* isolates recovered from patients with BSI, including IE.
- Ceftaroline particularly was active against MRSA from North American medical centers.
- Ceftaroline nonsusceptible MRSA isolates from patients with IE had a ceftaroline MIC of 2 mg/L, and results from a phase 3 randomized, controlled non-inferiority trial showed that ceftaroline fosamil 600 mg administered every 8 hours with 2-hour infusions can provide adequate exposure against *S. aureus* with ceftaroline MIC values of ≤4 µg/mL when treating ABSSSI.
- These results support further investigations to determine the role of ceftaroline in the treatment of IE.

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Table 1. Antimicrobial activity of ceftaroline and comparator agents tested against *S. aureus* from infective endocarditis and bloodstream infections (2010–2019)

Antimicrobial agent/ infection type	MIC in mg/L		% Susceptible by region (no. of isolates)[a]			
	MIC_{50}	MIC_{90}	NA	EUR	LATAM-APAC	All Regions
Infective endocarditis			(124)	(213)	(59)	(396)
Ceftaroline	0.25	1	99.2	92.0	98.3	95.2
Oxacillin	0.5	>2	59.7	74.6	81.4	71.0
Dalbavancin	≤0.03	0.06	100.0	100.0	100.0	100.0
Daptomycin	0.25	0.5	100.0	100.0	100.0	100.0
Levofloxacin	≤0.5	>4	71.8	73.7	91.5	75.8
Linezolid	1	2	100.0	100.0	100.0	100.0
Minocycline	≤0.06	0.12	98.6	100.0	100.0	99.5
Teicoplanin	≤2	≤2	100.0	100.0	100.0	100.0
Tetracycline	≤0.5	≤0.5	94.4	94.8	83.1	92.9
TMP-SMX	≤0.5	≤0.5	99.2	100.0	94.9	99.0
Vancomycin	1	1	100.0	100.0	100.0	100.0
Bloodstream infections			(11,900)	(7,772)	(4,161)	(23,833)
Ceftaroline	0.25	1	98.1	95.4	91.1	96.0
Oxacillin	0.5	>2	56.4	74.4	64.8	63.7
Dalbavancin	≤0.03	0.06	>99.9	100.0	>99.9	>99.9
Daptomycin	0.25	0.5	99.9	>99.9	>99.9	99.9
Levofloxacin	≤0.5	>4	61.3	74.8	74.1	67.9
Linezolid	1	2	100.0	100.0	100.0	100.0
Minocycline	≤0.06	0.12	98.9	99.5	97.5	98.9
Teicoplanin	≤2	≤2	100.0	>99.9	100.0	>99.9
Tetracycline	≤0.5	1	95.6	92.4	85.1	92.7
TMP-SMX	≤0.5	≤0.5	97.9	99.4	96.3	98.1
Vancomycin	1	1	100.0	100.0	100.0	100.0

[a] Criteria as published by CLSI (CLSI, 2020). NA, North America; EUR, Europe; LATAM-APAC, Latin America and Asia-Pacific regions.
Abbreviation: TMP-SMX, Trimethoprim-sulfamethoxazole

Figure 1. Ceftaroline activity against MSSA and MRSA from North American patients with infective endocarditis

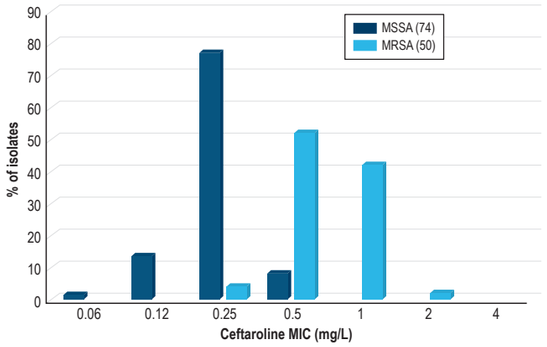

Figure 2. Ceftaroline activity against MSSA and MRSA from North American patients with bloodstream infections

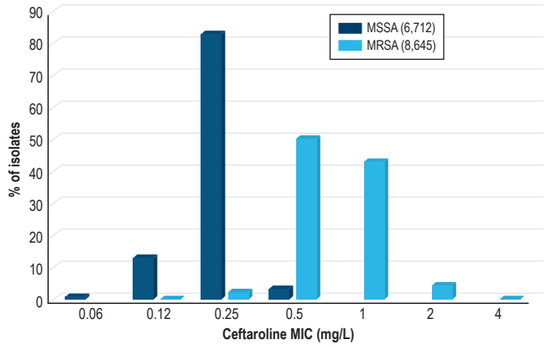

Figure 3. Yearly susceptibility rates for ceftaroline and oxacillin among *S. aureus* isolates from bloodstream infections in North America

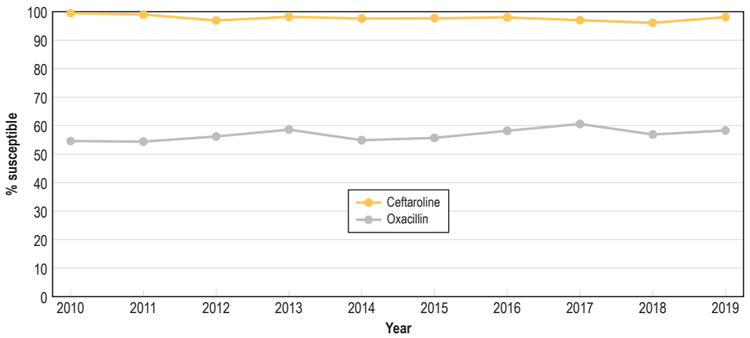

Table 2. Yearly susceptibility rates for ceftaroline (CPT) and oxacillin (OXA) stratified by region

Year (no. for all regions)	% Susceptible[a]					
	North America		Europe		LATAM-APAC[b]	
	CPT	OXA	CPT	OXA	CPT	OXA
2019 (1,614)	98.1	58.3	97.2	77.6	94.8	70.6
2018 (1,644)	96.1	56.9	94.8	75.9	96.8	71.8
2017 (1,960)	97.0	60.6	93.5	75.6	95.0	70.1
2016 (2,339)	98.0	58.2	97.1	72.8	93.4	72.3
2015 (2,167)	97.7	55.7	95.8	74.1	94.2	69.9
2014 (1,629)	97.6	54.9	91.8[c]	72.5	—[d]	—[d]
2013 (2,438)	98.2	58.6	95.5	78.2	88.9	60.6
2012 (2,119)	96.9	56.2	94.5	72.6	89.0	65.7
2011 (2,934)	99.0	54.4	95.2	71.4	88.1	59.7
2010 (4,989)	99.5	54.6	96.9	74.2	90.1	59.5

[a] Criteria as published by CLSI (CLSI, 2020).
[b] Include isolates from 26 countries located in Latin America and the Asia-Pacific region.
[c] Low susceptibility in Europe in 2014 mainly was due to low rates in Italy, Portugal, and Romania.
[d] Isolates from bloodstream infections were not collected in these regions in 2014.
Abbreviations: CPT, ceftaroline; OXA, oxacillin.