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Activity of Ceftobiprole Against *Enterococcus faecalis* Clinical Isolates From the United States (2016–2020), Including Those From Difficult-to-Treat Infections

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Introduction

- Ceftobiprole is an advanced-generation cephalosporin that has *in vitro* and *in vivo* activity against clinically important Gram-positive organisms, including MRSA, and Gram-negative organisms.
- While ceftobiprole does not have clinically relevant activity against *Enterococcus faecium*, ceftobiprole is active against *Enterococcus faecalis*, which is an opportunistic bacterial pathogen of clinical relevance and a significant cause of infective endocarditis.
- Ceftobiprole was approved in Europe and many non-European countries for the treatment of community-acquired bacterial pneumonia (CABP) and non–ventilator-associated hospital-acquired bacterial pneumonia in adults caused by indicated species, including *Streptococcus pneumoniae*.
- A New Drug Application for ceftobiprole was recently submitted to the United States (US) Food and Drug Administration seeking its approval for *Staphylococcus aureus* bacteremia, including right-sided infective endocarditis, acute bacterial skin and skin structure infections, and CABP.
- This study evaluated the *in vitro* antimicrobial activity of ceftobiprole and comparator agents against recent *E. faecalis* isolates responsible for various infections in patients from medical centers in the US.

Materials and Methods

Bacterial Isolates

- A total of 1,835 *E. faecalis* isolates from 34 US medical centers (2016–2020) in all 9 US Census Bureau Divisions were included in the surveillance program for ceftobiprole. Only 1 bacterial isolate per patient episode was selected.
- Isolates collected were responsible for bloodstream infections (40.8%), urinary tract infections (23.4%), skin and skin structure infections (22.0%), and other infection types (13.9%), including bone and joint infections (BJI; 1.6%), diabetic foot infections (DFI; 0.9%), and endocarditis (END; 0.8%).
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for antimicrobial susceptibility using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI-recommended quality control reference strains.
- Minimal inhibitory concentration (MIC) interpretations for ceftobiprole and comparators utilized European Committee on Antimicrobial Susceptibility Testing (EUCAST) and/or CLSI criteria. The EUCAST PK/PD non–species-related susceptible breakpoint of ≤4 mg/L was used for ceftobiprole.

Results

- In general, ceftobiprole inhibited 99.3% of all *E. faecalis* at ≤4 mg/L, whereas the comparator agents, ampicillin, daptomycin, linezolid, and vancomycin, inhibited between 97.0% to 100% of all isolates at their respective susceptible breakpoints (Tables 1 and 2).
- A total of 3% of all *E. faecalis* isolates were vancomycin resistant. Ceftobiprole had similar MIC_{50} results when tested against vancomycin-susceptible ($MIC_{50/90}$, 0.5/2 mg/L) and -resistant isolates ($MIC_{50/90}$, 2/4 mg/L), respectively (Tables 1 and 2).
  - Ampicillin, daptomycin, and linezolid were also active against vancomycin-susceptible and -resistant *E. faecalis* (Table 2).
- All isolates causing difficult-to-treat infections, such as bone and joint infections, diabetic foot infections and infective endocarditis, were inhibited by ceftobiprole at ≤4 mg/L (Table 1).
  - Ampicillin, daptomycin, and linezolid also inhibited these isolates at their respective susceptible breakpoints (Table 2).

Conclusions

- Ceftobiprole exhibited potent *in vitro* antimicrobial activity against *E. faecalis* clinical isolates collected in US medical centers (2016–2020).
  - Ceftobiprole was active regardless of the vancomycin phenotype or type of infection.
- These data suggest that ceftobiprole represents a potential option for empirical and guided treatment of infections caused by *E. faecalis* in US hospitals, including isolates causing difficult-to-treat infections.

Disclosures

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Table 1. Cumulative distributions of ceftobiprole MIC values for *E. faecalis* isolates (2016–2020)

Phenotype/Origin (No.)	Number and cumulative % of isolates at MIC (mg/L):									MIC50	MIC90
	0.03	0.06	0.12	0.25	0.5	1	2	4	>4		
All (1,834)	27 (1.5)	29 (3.1)	172 (12.4)	353 (31.7)	816 (76.2)	204 (87.3)	192 (97.8)	28 (99.3)	13 (100)	0.5	2
VAN-Susceptible (1,779)	27 (1.5)	29 (3.1)	171 (12.8)	348 (32.3)	807 (77.7)	192 (88.5)	170 (98.0)	24 (99.4)	11 (100)	0.5	2
VAN-Resistant (55)			1 (1.8)	5 (10.9)	9 (27.3)	12 (49.1)	22 (89.1)	4 (96.4)	2 (100)	2	4
BJI/DFI/END (61)		3 (4.9)	7 (16.4)	12 (36.1)	30 (85.2)	3 (90.2)	4 (96.7)	2 (100.0)		0.5	1

Abbreviations: MIC, minimal inhibitory concentration; VAN, vancomycin; BJI, bone and joint infections (n=29); DFI, diabetic foot infections (n=17); END, endocarditis (n=15).

Table 2. Activity of ceftobiprole and comparator antimicrobials against *E. faecalis* isolates (2016–2020)

Agent (No.)	MIC (mg/L)			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
All (1,834)									
Ceftobiprole	0.5	2	≤0.03 to >4				99.3		
Ampicillin	1	1	≤0.5 to 4	100		0.0	100	0.0	0.0
Daptomycin	1	1	≤0.25 to 4	99.2	0.8	0.0			
Levofloxacin	1	>4	≤0.03 to >4	79.2	0.2	20.6	79.4		20.6
Linezolid	1	2	0.25 to 8	99.7	0.2	0.1	99.9		0.1
Tetracycline	>16	>16	≤0.12 to >16	27.5	0.9	71.6			
Teicoplanin	≤0.5	≤0.5	≤0.5 to >16	97.2	0.0	2.8	97.2		2.8
Vancomycin	1	2	≤0.12 to >16	97.0	0.0	3.0	97.0		3.0
VAN-Susceptible (1,779)									
Ceftobiprole	0.5	2	≤0.03 to >4				99.4		
Ampicillin	1	1	≤0.5 to 4	100		0.0	100	0.0	0.0
Daptomycin	1	1	≤0.25 to 4	99.2	0.8	0.0			
Levofloxacin	1	>4	≤0.03 to >4	81.5	0.2	18.3	81.7		18.3
Linezolid	1	2	0.25 to 8	99.7	0.2	0.1	99.9		0.1
Tetracycline	>16	>16	≤0.12 to >16	28.2	0.8	71.0			
Teicoplanin	≤0.5	≤0.5	≤0.5 to 4	100	0.0	0.0	99.9		0.1
Vancomycin	1	2	≤0.12 to 4	100	0.0	0.0	100		0.0
VAN-Resistant (55)									
Ceftobiprole	2	4	0.12 to >4				96.4		
Ampicillin	1	2	≤0.5 to 2	100		0.0	100	0.0	0.0
Daptomycin	0.5	1	≤0.25 to 1	100	0.0	0.0			
Levofloxacin	>4	>4	1 to >4	5.6	0.0	94.4	5.6		94.4
Linezolid	1	2	0.5 to 2	100	0.0	0.0	100		0.0
Tetracycline	>16	>16	0.25 to >16	3.8	5.7	90.6			
Teicoplanin	>16	>16	0.5 to >16	7.3	0.0	92.7	7.3		92.7
Vancomycin	>16	>16	>16	0.0	0.0	100	0.0		100
BJI/DFI/END (61)									
Ceftobiprole	0.5	1	0.06 to 4				100		
Ampicillin	1	1	≤0.5 to 2	100		0.0	100	0.0	0.0
Daptomycin	1	1	≤0.25 to 2	100	0.0	0.0			
Levofloxacin	1	>4	0.25 to >4	85.2	0.0	14.8	85.2		14.8
Linezolid	1	2	0.25 to 2	100	0.0	0.0	100		0.0
Tetracycline	>16	>16	≤0.12 to >16	26.2	1.6	72.1			
Teicoplanin	≤0.5	≤0.5	≤0.5 to >16	98.4	0.0	1.6	98.4		1.6
Vancomycin	1	2	0.5 to >16	98.4	0.0	1.6	98.4		1.6

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible; VAN, vancomycin; BJI, bone and joint infections (n=30); DFI, diabetic foot infections (n=17); END, endocarditis (n=15).
[a] Criteria as published by CLSI (2023) and EUCAST (2023). For ceftobiprole, the EUCAST PK/PD non-species-related susceptible breakpoint of ≤4 mg/L was used.

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