IDWeek 2023 | Poster #2162

In Vitro Antimicrobial Activity of Ceftobiprole against *Streptococcus pneumoniae* Isolates from the United States (2016–2020)

Leonard Duncan[1], Mariana Castanheira[1], Jennifer I Smart[2], Mark E Jones[2], Rodrigo E Mendes[1]

[1] JMI Laboratories, North Liberty, Iowa, USA; [2] Basilea Pharmaceutica International Ltd., Allschwil, Switzerland

Introduction

- Ceftobiprole is an advanced-generation cephalosporin 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*.
- Ceftobiprole exhibits bactericidal activity against Gram-positive species, including *S. pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA), via inhibition of cell-wall synthesis.
  - Ceftobiprole exhibits high affinity for multiple penicillin-binding proteins and a low propensity for resistance development.
- A New Drug Application for ceftobiprole was recently submitted to the United States (US) Food and Drug Administration seeking its approval for *S. 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 *S. pneumoniae* isolates causing lower respiratory tract infections in patients from medical centers in the US.

Materials and Methods

- A total of 2,793 *S. pneumoniae* isolates from 32 US medical centers (2016–2020) in all 9 US Census Bureau Divisions (Figure 1) were collected from patients with lower respiratory tract infections.
- Isolates were tested for antimicrobial susceptibility using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method with appropriate quality controls.
- Only 1 bacterial isolate per patient episode was collected.
- Minimal inhibitory concentration (MIC) interpretations for ceftobiprole and comparators utilized European Committee on Antimicrobial Susceptibility Testing (EUCAST) or CLSI criteria, respectively.
- The EUCAST ceftobiprole susceptibility breakpoint for *S. pneumoniae* was 0.5 mg/L.

Results

- Ceftobiprole inhibited 99.5 percent of all *S. pneumoniae* isolates at the EUCAST breakpoint ($MIC_{50/90}$, 0.015/0.25 mg/L; Table 1).
  - % susceptibility ranged from 98.9–99.7% over the 5-year period from 2016–2020.
    - MIC_{50} values were 0.015 mg/L each year.
    - MIC_{90} values ranged from 0.25–0.5 mg/L during the same 5-year period.
- Ceftobiprole activity varied little by US Census Division (Figure 1).
- The following comparator agents displayed lower activity against the full isolate set (CLSI criteria; Table 2):
  - clindamycin (85.5% susceptible),
  - erythromycin (53.2% susceptible),
  - penicillin (63.2% susceptible using oral breakpoints),
  - tetracycline (79.4% susceptible), and
  - trimethoprim-sulfamethoxazole (72.8% susceptible).
- Ceftobiprole maintained potent *in vitro* activity (i.e., >95% susceptible) against each of the isolate subsets resistant to the comparator antimicrobials (Figure 2).
  - 95.4–98.8% susceptible to ceftobiprole depending on the comparator antimicrobial.
  - 95.4% of the penicillin-resistant isolates were susceptible to ceftobiprole.
  - Ceftobiprole activity was low against the ceftriaxone-resistant isolate subset [9.1% susceptible (not shown); n=11, using non-meningitis breakpoints].
- This *S. pneumoniae* isolate set was also 99.4% susceptible to levofloxacin, 97.4% susceptible to ceftriaxone (using non-meningitis breakpoints), and 100% susceptible to linezolid and vancomycin (Table 2).

Conclusions

- Ceftobiprole exhibited potent *in vitro* antimicrobial activity against recent *S. pneumoniae* clinical isolates collected in US medical centers (2016–2020).
  - Ceftobiprole $MIC_{50/90}$ values and % susceptible values remained stable during the 5-year surveillance period.
  - Ceftobiprole maintained potent *in vitro* activity against isolate subsets resistant to clindamycin, erythromycin, penicillin, tetracycline, or trimethoprim-sulfamethoxazole.
- These *in vitro* data suggest that ceftobiprole may be a potential option for the treatment of lower respiratory tract infections caused by *S. pneumoniae* in the US.

Disclosures

This project was funded in part with federal funds from the Department of Health and Human Services, Administration for Strategic Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), under contract no. HHSO100201600002C, and in part by Basilea Pharmaceutica International Ltd., Allschwil, Switzerland. JMI Laboratories received compensation for services in relation to preparing the poster.

Figure 1. Ceftobiprole activity and number of isolates by US Census Bureau Division

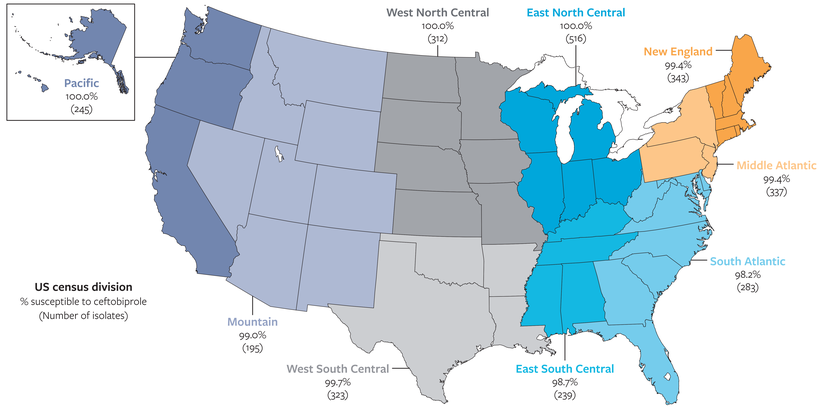
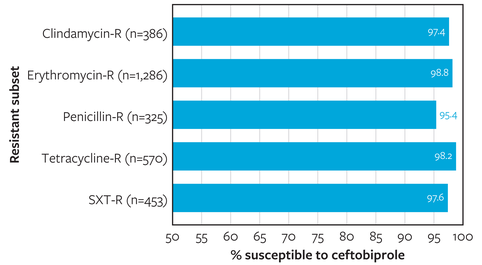


Figure 2. Ceftobiprole activity against drug-resistant isolate subsets



Abbreviations: CLSI, Clinical and Laboratory Standards Institute; R, resistant; SXT, trimethoprim-sulfamethoxazole.
CLSI (2023) breakpoints were utilized (oral breakpoint for penicillin) to categorize isolates except for ceftobiprole, for which the EUCAST susceptibility breakpoint (0.5 mg/L) was used.

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

Year	Number of isolates	Number and cumulative % of isolates at MIC (mg/L): 0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	MIC_{50}	MIC_{90}	%S
All years	2,793	5 0.2	15 0.7	79 3.5	791 31.9	904 64.2	109 68.1	123 72.5	160 78.3	338 90.4	254 99.5	13 99.9	2 100	0.015	0.25	99.5
2016	599	0 0.0	1 0.2	9 1.7	141 25.2	222 62.3	25 66.4	29 71.3	33 76.8	65 87.6	72 99.7	2 100		0.015	0.5	99.7
2017	557	1 0.2	4 0.9	16 3.8	144 29.6	183 62.5	25 67.0	20 70.6	33 76.5	68 88.7	61 99.6	2 100		0.015	0.5	99.6
2018	620	2 0.3	3 0.8	21 4.2	207 37.6	170 65.0	21 68.4	31 73.4	36 79.2	78 91.8	48 99.5	1 99.7	2 100	0.015	0.25	99.5
2019	550	1 0.2	3 0.7	12 2.9	164 32.7	179 65.3	22 69.3	23 73.5	32 79.3	68 91.6	43 99.5	3 100		0.015	0.25	99.5
2020	467	1 0.2	4 1.1	21 5.6	135 34.5	150 66.6	16 70.0	20 74.3	26 79.9	59 92.5	30 98.9	5 100		0.015	0.25	98.9

Abbreviations: MIC, minimal inhibitory concentration; S, susceptible, using the EUCAST breakpoint of 0.5 mg/L.

Table 2. Activity of ceftobiprole and comparator antimicrobials against all 2,793 *S. pneumoniae* isolates (2016–2020)

Antimicrobial agent	MIC (mg/L) MIC_{50}	MIC_{90}	MIC range	CLSI [a] %S	%I	%R	EUCAST [a] %S	%I	%R
Ceftobiprole	0.015	0.25	≤0.001 to 2				99.5		0.5
Ceftriaxone	0.03	1	≤0.015 to >2	97.4 [b]	2.2	0.4	86.6 [b]	13.0	0.4
Clindamycin	≤0.25	>2	≤0.25 to >2	85.5	0.6	13.8	86.2		13.8
Erythromycin	0.06	>16	≤0.015 to >16	53.2	0.7	46.0	53.2		46.8
Levofloxacin	1	1	≤0.06 to >4	99.4	0.1	0.5	[c]	99.4	0.6
Linezolid	1	2	≤0.12 to 2	100.0			100.0		0.0
Penicillin	0.03	2	≤0.008 to >4	63.2 [d] 96.6 [e]	25.2 3.0	11.6 0.4	63.2 [b]	33.4	3.4
Tetracycline	≤0.25	>4	≤0.25 to >4	79.4	0.2	20.4	79.4		20.6
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	72.8	10.9	16.2	78.3	5.5	16.2
Vancomycin	0.25	0.5	≤0.06 to 0.5	100.0			100.0		0.0

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible.
[a] Criteria as published by CLSI (2023) and EUCAST (2023).
[b] Using non-meningitis breakpoints.
[c] EUCAST indicates that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible, increased exposure.
[d] Using oral breakpoints.
[e] Using parenteral, non-meningitis breakpoints.

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Contact

element

Rodrigo E. Mendes, Ph.D., FIDSA
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: rodrigo.mendes@element.com

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