ASM Microbe 2019 | Poster Saturday-AAR-780

Ceftibuten-Clavulanate Activity against Extended-Spectrum β-Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae*

Helio S. Sader, Lalitagauri M. Deshpande, Timothy B. Doyle, Rodrigo E. Mendes, Mariana Castanheira
JMI Laboratories, North Liberty, Iowa, USA

Introduction

- Ceftibuten is an orally active third-generation cephalosporin that has a broad spectrum of *in vitro* antibacterial activity, encompassing most gram-negative pathogens and streptococci and shows greater stability than several other cephalosporins against bacteria producing extended-spectrum β-lactamases (ESBLs)
- Clavulanate potentiates penicillins and cephalosporins against β-lactamase-producing *Enterobacterales* bacteria by inhibiting sensitive β-lactamases, thus allowing the companion β-lactam to kill the bacteria
- The clavulanate spectrum comprises most class A β-lactamases, including ESBLs and, to a lesser extent, serine carbapenemases
- The ceftibuten-clavulanate combination is being developed for the treatment of urinary tract infections (UTIs)
- In this study, we evaluated the antimicrobial susceptibility and frequency of occurrence of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in the United States (USA) and other regions

Materials and Methods

- A total of 856 ESBL-producing *E. coli* (n=406) and *K. pneumoniae* (n=450) isolates were collected in 2017 in medical centers located in the USA (n=169; 27 centers), Europe (EUR; n=318; 34 centers in 17 nations), Asia-Pacific (APAC; n=169; 13 centers in 7 nations), and Latin America (LATAM; n=200; 6 centers in 6 nations; Figure 1)
- Ceftibuten-clavulanate (2:1 ratio) and comparator agents were susceptibility tested by reference broth microdilution methods at a central laboratory (JMI Laboratories, North Liberty, Iowa, USA)
- Percentages of isolates inhibited at ≤4 mg/L of ceftibuten-clavulanate were evaluated for comparison
- Categorical interpretations from the Clinical and Laboratory Standards Institute (CLSI) and/or US Food and Drug Administration breakpoint tables were applied for comparator agents, when available
- Quality control (QC) was performed according to CLSI guidelines (M07)

Results

- The ESBL-producing rates among *E. coli* were 14.2% in the USA, 17.4% in EUR, 23.7% in APAC, and 33.7% in LATAM, and among *K. pneumoniae* were 11.9% in the USA, 31.5% in EUR, 29.3% in APAC, and 31.8% in LATAM (Figure 2)
- The most frequent ESBLs were CTX-M types among *E. coli* (97.8% of isolates) and *K. pneumoniae* (93.8%)
- Among ESBL-producing *K. pneumoniae*, SHV types were observed in 11.8% of isolates and 6.9% had both CTX-M- and SHV types
- Ceftibuten-clavulanate inhibited 93.8% and 90.2% of ESBL-producing *E. coli* and *K. pneumoniae*, respectively, at MICs of ≤4 mg/L (Table 1 and Figures 3 and 4), whereas amoxicillin-clavulanate was active against 47.8% and 20.7%, respectively (Table 1)
- Among other oral agents, levofloxacin was active against 19.0% and 26.0% for *E. coli* and *K. pneumoniae*, respectively, and susceptibility rates for cefuroxime and cefpodoxime were null (0.0%; Table 1 and Figures 3 and 4)
- Trimethoprim-sulfamethoxazole (TMP-SMX) exhibited very limited activity against ESBL-producing *E. coli* and *K. pneumoniae* (Table 1 and Figures 3 and 4)

Conclusions

- Ceftibuten-clavulanate was the most active oral agent tested against ESBL-producing *E. coli* and *K. pneumoniae* isolates collected worldwide in 2017
- ESBL rates and antimicrobial susceptibility of ESBL-producing isolates varied among geographic regions
- The results of this investigation support further clinical development of ceftibuten-clavulanate for treatment of infections caused by ESBL-producing *E. coli* and *K. pneumoniae* isolates

Acknowledgements

This study was performed by JMI Laboratories and supported by Achaogen, which included funding for preparing this poster.

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Contact

Helio S. Sader, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

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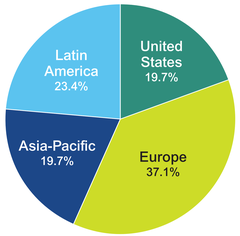
Figure 1 Distribution of ESBL-producing *E. coli* and *K. pneumoniae* isolates by geographic region



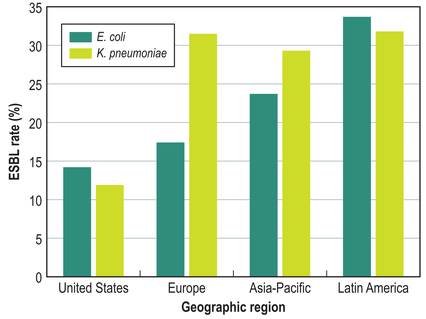
ESBL, extended-spectrum β-lactamase

Table 1. Antimicrobial activity of ceftibuten-clavulanate and comparator agents tested against 856 ESBL-poducing *Enterobacterales* isolates

Antimicrobial agent	MIC_{50}[a]	MIC_{90}[a]	% susceptible[b] (no. of isolates)				
			USA	EUR	APAC	LATAM	All
ESBL-producing *E. coli*			(92)	(113)	(83)	(118)	(406)
Ceftibuten-clavulanate (2:1)	0.5	2	[95.7][c]	[97.3][c]	[90.4][c]	[91.5][c]	[93.8][c]
Cefpodoxime	>64	>64	0.0	0.0	0.0	0.0	0.0
Cefuroxime	>64	>64	0.0[d]	0.0[d]	0.0[d]	0.0[d]	0.0[d]
Amoxicillin-clavulanate	16	32	52.2	35.4	63.9	44.9	47.8
TMP-SMX	>8	>8	33.7	31.9	36.1	32.2	33.3
Levofloxacin	16	>16	14.1	17.9	28.9	16.9	19.0
Meropenem	0.03	0.06	98.9	99.1	100.0	99.2	99.3
ESBL-producing *K. pneumoniae*			(77)	(205)	(86)	(82)	(450)
Ceftibuten-clavulanate (2:1)	0.25	4	[96.1][c]	[85.4][c]	[89.5][c]	[97.6][c]	[90.2][c]
Cefpodoxime	>64	>64	0.0	0.0	0.0	0.0	0.0
Cefuroxime	>64	>64	0.0[d]	0.0[d]	0.0[d]	0.0[d]	0.0[d]
Amoxicillin-clavulanate	16	32	37.7	15.1	20.9	18.3	20.7
TMP-SMX	>8	>8	19.5	11.2	18.6	9.8	13.8
Levofloxacin	8	>16	32.5	37.1	24.4	31.7	26.0
Meropenem	0.03	0.25	94.8	86.8	100.0	98.8	92.9

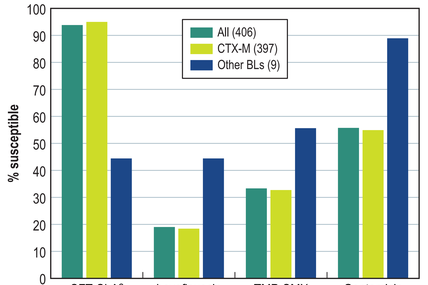
USA, United States; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America; ESBL, extended-spectrum β-lactamase; TMP-SMX, trimethoprim-sulfamethoxazole
[a] MIC_{50} and MIC_{90} values (mg/L) for isolates from all regions combined.
[b] Criteria as published by CLSI (2019).
[c] Percentage inhibited at ≤4 mg/L in brackets for comparison.
[d] Oral breakpoints (CLSI, 2019).

Figure 2 ESBL-producing rates stratified by geographic region



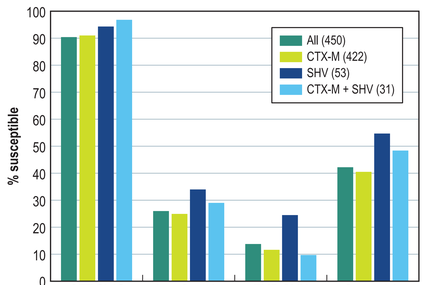
ESBL, extended-spectrum β-lactamase

Figure 3 Susceptibility rates for ESBL-producing *E. coli* isolates from all geographic regions combined and stratified by β-lactamase type



[a] Percentage inhibited at ≤4 mg/L.
ESBL, extended-spectrum β-lactamase; CFT-CLA, ceftibuten-clavulanate; TMP-SMX, trimethoprim-sulfamethoxazole.

Figure 4 Susceptibility rates for ESBL-producing *K. pneumoniae* isolates from all geographic regions combined and stratified by β-lactamase type



[a] Percentage inhibited at ≤4 mg/L.
ESBL, extended-spectrum β-lactamase; CFT-CLA, ceftibuten-clavulanate; TMP-SMX, trimethoprim-sulfamethoxazole.