ASM Microbe 2019 | Poster Sunday-AAR-718

# Antimicrobial Activity of Ceftibuten-Clavulanate When Tested against Clinical *Enterobacterales* Isolates Collected Worldwide in 2017

**Helio S. Sader, Jennifer M. Streit, S.J. Ryan Arends, Cecilia G. Carvalhaes, 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
- The ceftibuten-clavulanate combination is being developed for the treatment of urinary tract infections (UTIs)
- In this study, we evaluated the activity of the ceftibuten-clavulanate combination (2:1 ratio) and comparator antimicrobial agents against clinical *Enterobacterales* isolates collected worldwide in 2017

## Materials and Methods

- A total of 5,658 *Enterobacterales* isolates were collected in 2017, including 2,051 from the United States (USA; 31 centers), 1,966 from Europe (EUR; 37 centers in 18 nations), 860 from the Asia-Pacific region (APAC; 13 centers in 7 nations), and 781 from Latin America (LATAM; 9 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), and all QC MIC results were within acceptable ranges as published in CLSI documents

## Results

- Isolates were mainly from bacteremia (28.2%), UTIs (23.3%), pneumonia (20.6%), skin and skin structure infections (SSSIs; 16.0%), intra-abdominal infections (IAIs; 10.8%), and others (1.0%; Figure 2)
- Ceftibuten-clavulanate was very active against *Enterobacterales* with $MIC_{50/90}$ values of 0.25/4 mg/L and percentages inhibited at ≤4 mg/L varying from 88.3% in LATAM to 93.3% in the USA (91.0% overall; Tables 1 and 2 and Figure 3)
- The most ceftibuten-clavulanate-susceptible *Enterobacterales* species were *Proteus vulgaris* and *Providencia rettgeri* (both with $MIC_{50/90}$, ≤0.03/≤0.03 mg/L), followed by *Proteus mirabilis* ($MIC_{50/90}$, ≤0.03/0.06 mg/L), and then *Klebsiella oxytoca*, *Citrobacter koseri*, and *Providentia stuartii*, all 3 with $MIC_{50/90}$ of ≤0.03/0.12 mg/L (Table 1)
- Overall susceptibility of *Enterobacterales* to the oral agents cefpodoxime, cefuroxime, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, and levofloxacin were 69.0%, 52.9%, 61.2%, 69.9%, and 73.9%, respectively (Table 2 and Figure 3)
- Ceftibuten-clavulanate retained good activity against most ceftriaxone-nonsusceptible *Escherichia coli* ($MIC_{50/90}$, 0.5/32 mg/L), with percentages inhibited at ≤4 mg/L, varying from 80.0% in the APAC region to 91.9% in Europe (85.6% overall; Table 2)
- Ceftibuten-clavulanate activity against ceftriaxone-nonsusceptible *Klebsiella pneumoniae* were highest in the USA (85.3% inhibited at ≤4 mg/L) and lowest in LATAM (66.7% inhibited at ≤4 mg/L; Table 2)

## Conclusions

- Ceftibuten-clavulanate was the most active oral agent tested against *Enterobacterales* isolates collected worldwide in 2017
- Ceftibuten-clavulanate activity varied among *Enterobacterales* species and geographic regions
- Results of this investigation support further clinical development of ceftibuten-clavulanate for treatment of *Enterobacterales* infections

## Acknowledgements

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

## References

- CLSI. M07. Methods for dilution antimicrobial susceptibilty tests for bacteria that grow aerobically; approved standard - eleventh edition. Wayne, PA, Clinical and Laboratory Standards Institute, 2018.
- CLSI. M100. Performance standards for antimicrobial susceptibility testing: 29th informational supplement. Wayne, PA, Clinical and Laboratory Standards Institute, 2019.
- Hunter PA, Coleman K, Fisher J and Taylor D. *In vitro* synergistic properties of clavulanic acid, with ampicillin, amoxycillin and ticarcillin. *J. Antimicrob. Chemother.* 6: 455-470: 1980.
- Jones RN. Ceftibuten: a review of antimicrobial activity, spectrum and other microbiologic features. *Pediatr. Infect. Dis. J.* 14: S77-83: 1995.
- Kresken M, Korber-Irrgang B, Biedenbach DJ, Batista N, Besard V, Canton R, Garcia-Castillo M, Kalka-Moll W, Pascual A, Schwarz R, Van Meensel B, Wisplinghoff H and Seifert H. Comparative *in vitro* activity of oral antimicrobial agents against *Enterobacteriaceae* from patients with community-acquired urinary tract infections in three European countries. *Clin. Microbiol. Infect.* 22: 63 e61-63 e65: 2016.
- Neu HC. Ceftibuten: minimal inhibitory concentrations, postantibiotic effect and beta-lactamase stability—a rationale for dosing programs. *Pediatr. Infect. Dis. J.* 14: S88-92: 1995.

**Figure 1. Isolate distribution by geographic region**

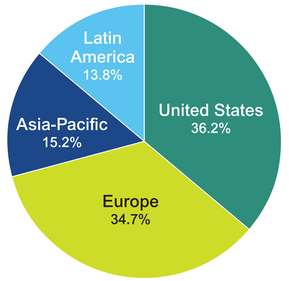



**Figure 2. Isolate distribution by infection type**

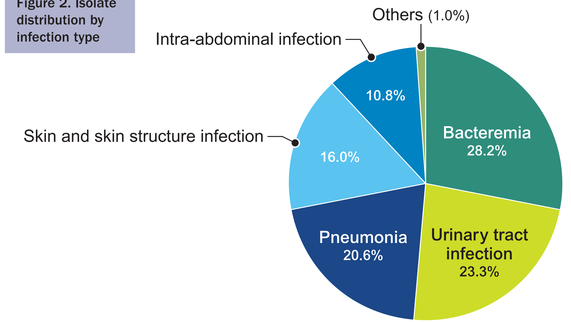
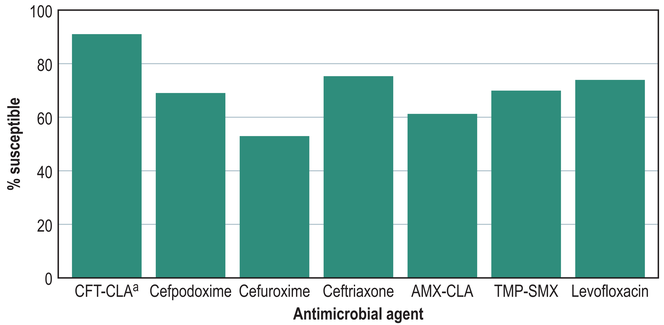



**Figure 3. Susceptibility rates for *Enterobacterales* isolates from all geographic regions combined**




[a] Percentage inhibited at ≤4 mg/L.
CFT-CLA, ceftibuten-clavulanate; AMX-CLA, amoxicillin-clavulanate, TMP-SMX, trimethoprim-sulfamethoxazole

**Table 1 Antimicrobial activity of ceftibuten-clavulanate tested against the most common *Enterobacterales* species stratified by geographic region**

| Organism (no. tested) | $MIC_{50}/MIC_{90}$ (% inhibited at ≤4 mg/L of ceftibuten-clavulanate) USA | EUR | APAC | LATAM | All |
|---|---|---|---|---|---|
| *Enterobacterales* (5,568) | 0.12/2 (93.3) | 0.25/4 (90.4) | 0.25/8 (89.2) | 0.25/8 (88.3) | 0.25/4 (91.0) |
| *E. coli* (2,000) | 0.25/1 (95.7) | 0.25/1 (96.6) | 0.25/1 (93.4) | 0.25/1 (94.6) | 0.25/1 (95.4) |
| *K. pneumoniae* (1,850) | 0.06/0.25 (97.7) | 0.12/8 (87.7) | 0.06/16 (87.4) | 0.12/32 (82.9) | 0.06/4 (90.5) |
| *K. oxytoca* (346) | ≤0.03/0.12 (100.0) | ≤0.03/0.12 (99.3) | ≤0.03/0.12 (96.7) | ≤0.03/1 (100.0) | ≤0.03/0.12 (99.4) |
| Indole-positive Proteeae (331)[a] | 0.06/8 (88.4) | 0.06/8 (89.7) | 0.12/8 (84.0) | 0.25/32 (76.0) | 0.06/8 (87.6) |
| *C. freudii* (228) | 2/64 (78.4) | 2/64 (68.6) | 4/64 (50.0) | 2/64 (71.4) | 2/64 (73.2) |
| *P. mirabilis* (210) | ≤0.03/0.06 (96.0) | ≤0.03/0.06 (93.3) | ≤0.03/≤0.03 (100.0) | ≤0.03/≤0.03 (93.3) | ≤0.03/0.06 (95.2) |
| *E. cloacae* (180) | 2/64 (61.7) | 2/64 (61.7) | 2/64 (66.7) | 1/64 (63.3) | 2/64 (62.8) |
| *S. marcescens* (180) | 0.25/0.5 (96.7) | 0.25/4 (91.7) | 0.25/1 (93.3) | 0.25/2 (93.3) | 0.25/2 (93.9) |
| *C. koseri* (170) | ≤0.03/0.12 (100.0) | 0.06/0.12 (100.0) | ≤0.03/0.12 (100.0) | ≤0.03/— (100.0) | ≤0.03/0.12 (100.0) |
| *K. aerogenes* (163) | 1/64 (63.3) | 0.5/32 (70.0) | 0.5/64 (65.5) | 0.5/1 (92.9) | 1/64 (68.7) |

USA, United States; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America
[a] Includes: *M. morganii* (176), *P. vulgaris* (17), *P. vulgaris* group (56), *P. rettgeri* (33), *P. stuartii* (49)
[b] Only 9 isolates tested.

**Table 2 Antimicrobial activity of ceftibuten-clavulanate and comparator agents tested against 5,658 *Enterobacterales* isolates**

| Organism group / Antimicrobial agent | $MIC_{50}$[a] | $MIC_{90}$[a] | % susceptible[b] (no. of isolates) USA | EUR | APAC | LATAM | All |
|---|---|---|---|---|---|---|---|
| All isolates | | | (2,051) | (1,966) | (860) | (781) | (5,658) |
| Ceftibuten-clavulanate (2:1) | 0.25 | 4 | [93.3][c] | [90.4][c] | [89.2][c] | [88.3][c] | [91.0][c] |
| Cefpodoxime | 0.5 | >64 | 76.8 | 67.5 | 65.2 | 56.6 | 69.0 |
| Cefuroxime | 4 | >64 | 59.6[d] | 51.0[d] | 51.6[d] | 41.4[d] | 52.9[d] |
| Ceftriaxone | ≤0.06 | >8 | 84.3 | 73.4 | 70.7 | 61.8 | 75.3 |
| Amoxicillin-clavulanate | 8 | >32 | 67.2 | 57.0 | 63.0 | 53.8 | 61.2 |
| TMP-SMX | ≤0.5 | >8 | 79.4 | 68.9 | 66.6 | 51.3 | 69.9 |
| Levofloxacin | 0.06 | 16 | 80.7 | 72.4 | 73.8 | 59.9 | 73.9 |
| Ceftriaxone-nonsusceptible *E. coli* | | | (105) | (124) | (95) | (127) | (451) |
| Ceftibuten-clavulanate (2:1) | 0.5 | 32 | [83.8][c] | [91.9][c] | [80.0][c] | [85.0][c] | [85.6][c] |
| Cefpodoxime | >64 | >64 | 0.0 | 0.0 | 1.1 | 0.0 | 0.2 |
| Cefuroxime | >64 | >64 | 1.0[d] | 0.0[d] | 1.1[d] | 0.0[d] | 0.4[d] |
| Amoxicillin-clavulanate | 16 | >32 | 45.7 | 33.9 | 56.8 | 41.7 | 43.7 |
| TMP-SMX | >8 | >8 | 35.2 | 32.3 | 35.8 | 30.7 | 33.3 |
| Levofloxacin | 16 | >16 | 18.1 | 21.1 | 34.7 | 17.3 | 22.2 |
| Ceftriaxone-nonsusceptible *K. pneumoniae* | | | (95) | (279) | (117) | (132) | (623) |
| Ceftibuten-clavulanate (2:1) | 0.5 | 32 | [85.3][c] | [71.3][c] | [70.9][c] | [66.7][c] | [72.4][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 | 32.6 | 11.5 | 16.2 | 11.4 | 15.6 |
| TMP-SMX | >8 | >8 | 20.0 | 14.3 | 14.5 | 9.8 | 14.3 |
| Levofloxacin | 8 | >16 | 29.5 | 18.3 | 20.5 | 22.7 | 21.3 |

USA, United States; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America; 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).

## 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

To obtain a PDF of this poster:

Scan the QR code or visit https://www.jmilabs.com/data/posters/ASM-Microbe19-ceftibuten-clavulanate-2017.pdf

Charges may apply. No personal information is stored.