# #03502 Ceftibuten-avibactam as an oral alternative to ceftazidime-avibactam for serine carbapenemase-producing Enterobacterales

03. Bacterial susceptibility & resistance
03b. Resistance surveillance & epidemiology: Healthcare-associated bacteria

M. Echegorry[1], L. Maccari[1], G. Di Carlo[1], M.A. Menocal[1], J. De Mendieta[1], M. Rapoport[1], C. Lucero[1], P. Ceriana[1], A. Corso[1], F. Pasteran[1].
*[1]Servicio de Antimicrobianos, Laboratorio Nacional de Referencia en Antimicrobianos INEIA ANLIS Dr Carlos G. Malbran - Buenos Aires (Argentina)*

## Background

CPEs represent a major global public health threat, owing to their limited therapeutic options and high morbidity and mortality. Avibactam (AVI) is a non-β-lactam inhibitor active against class A (ESBL, KPC), class C, and some class D β-lactamases (OXA-48-like as OXA-163). An oral pro-drug formulation of AVI has been partnered with ceftibuten (CTB), an oral third-generation cephalosporin. This combination is being developed as an oral alternative to intravenous ceftazidime-avibactam (CZA) for the treatment of complicated urinary tract infections due to serine-carbapenemase producing Enterobacterales (SCPE).

Aim: to assess the in vitro activity of CTB vs. CTB-AVI susceptibility against SCPE clinical isolates.

## Methods

Clinical isolates from a National Prevalence Survey (RECAPT-AR; 181 hospitals) were analyzed. A panel of 408 well-defined by PCR/WGS SCPE (327 blaKPC, 61 blaOXA-163 and 20 blaKPC plus blaOXA-163) and 4 ATCC strains were included. MICs were determined by broth microdilution for CTB, CTB-AVI and CZA, following CLSI guidelines. Susceptibility data for other oral urinary options (ciprofloxacin-CIP- and trimethoprim/sulfamethoxazole-TMS-) were obtained by disk diffusion/automatic methods. AVI was tested at a fixed concentration of 4 mg/L. CTB susceptible breakpoints currently published by EUCAST (≤ 1 mg/L) and CLSI (≤ 8 mg/L) were applied to CTB-AVI for comparison.

## Results

MIC50/MIC90 and susceptibility rates by carbapenemase class are shown in Fig.1. Cumulative MICs for CTB vs. CTB-AVI are depicted in Fig.2. At concentrations of ≤1/4 and ≤8/4 mg/L (preliminary susceptible category), CTB-AVI inhibited 95.1%/98.8% of KPC, 78.7%/88.5% of OXA-163 and 90.0%/100% of KPC plus OXA-163 producing isolates. Susceptibility to CTB-AVI was equivalent to CZA across all SCPE ($p>0.05$). Conversely, CTB-AVI outperformed CIP and TMS ($p<0.002$). A cluster of OXA-163 producing

Escherichia coli was identified in one of the 24 jurisdictions, which exhibited high-level resistance to CTB-AVI (Fig.3).

## Conclusions

CTB-AVI exhibits excellent in vitro activity against SCPE achieving susceptibility rates comparable to those of CZA. Its favorable oral bioavailability, coupled with robust activity against high-priority carbapenemase producers, places CTB-AVI as a highly promising candidate for effective non-intravenous treatment and step-down therapy of infections caused by these difficult-to-treat pathogens.

**Fig.1** CTB-AVI and comparators susceptibility rates, $MIC_{50}$/$MIC_{90}$ and MIC ranges for SCPE

| CBP | n | CTB | | | | | CTB-AVI | | | | | CZA | | | | CIP | TMS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $CIM_{50}$ (mg/L) | $CIM_{90}$ (mg/L) | %S EUCAST | %S CLSI | Range (mg/L) | $CIM_{50}$ (mg/L) | $CIM_{90}$ (mg/L) | %S EUCAST | %S CLSI | Range (mg/L) | $CIM_{50}$ (mg/mL) | $CIM_{90}$ (mg/L) | %S EUCAST/ CLSI | Range (mg/L) | %S | %S |
| KPC | 327 | 32 | >64 | 3,1 | 26,9 | 0.5 - >64 | 0,06 | 0,5 | 95,1 | 98,8 | <=0.03 - 64 | 0,5 | 1 | 97,2 | <=0.5 - >32 | 8.3 | 14.9 |
| OXA | 61 | 64 | >64 | 4,9 | 13,1 | 0.25 - >64 | 0,25 | 64 | 78,7 | 88,5 | <=0.03 - 64 | 2 | 4 | 95,1 | <=0.25 - 64 | 10.2 | 13.6 |
| KPC + OXA | 20 | 64 | >64 | 0 | 5 | 16 - >64 | 0,25 | 1 | 90 | 100 | <=0.03 - 2 | 1 | 2 | 100 | <=0.25 - 2 | 5.0 | 0.0 |
| TOTAL | 408 | 32 | >64 | 3,2 | 23,7 | 0.25 - >64 | 0,06 | 1 | 92,9 | 97,3 | <=0.03 - 64 | <0,5 | 2 | 97,8 | <=0.25 - 64 | 8.4 | 14.3 |

CTB: ceftibuten, CTB-AVI: ceftibuten-avibactam, CZA: ceftazidime-avibactam; CIP: ciprofloxacin, TMS: trimethoprim/sulfamethoxazole, %S: susceptible, Panel included (n): *K. pneumoniae* (324), *Enterobacter cloacae* (33), *Escherichia coli* (17), *Serratia marcescens* (12), *Morganellaceae*,(9) *Klebsiella aerogenes (7), Klebsiella oxytoca* (2), *Citrobacter freundii* (2) and 1 *Citrobacter koseri* (1).

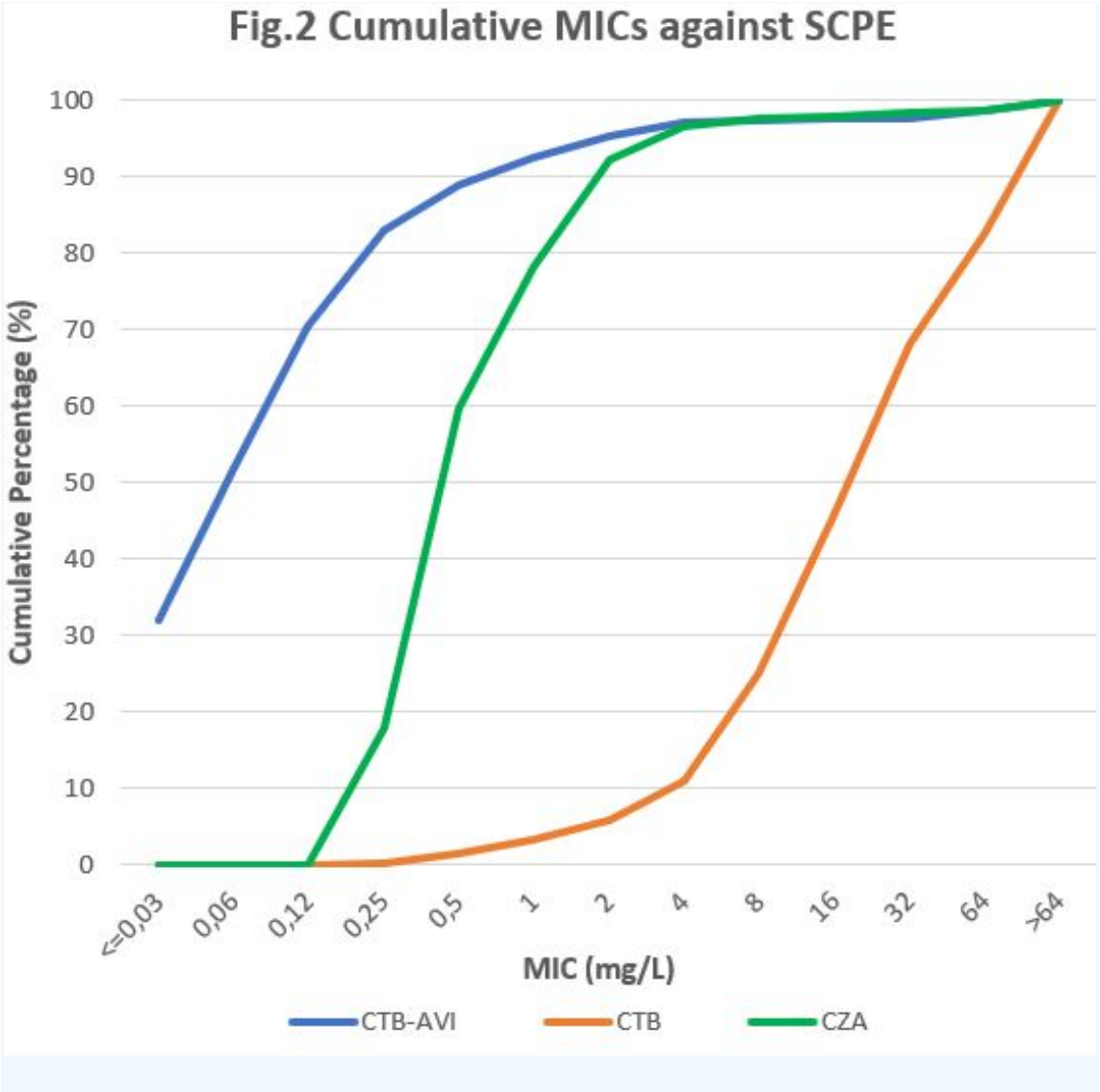
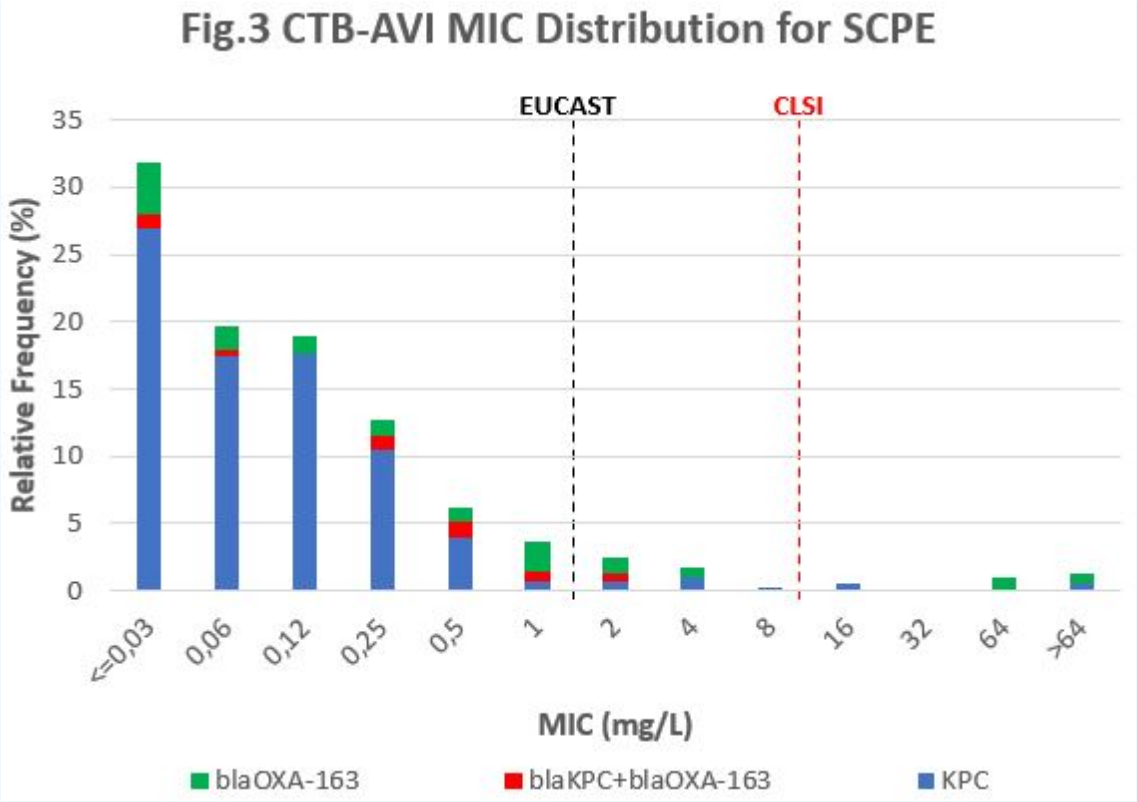


Fig.2 Cumulative MICs against SCPE
Cumulative Percentage (%)
100
90
80
70
60
50
40
30
20
10
0
<=0,03
0,06
0,12
0,25
0,5
1
2
4
8
16
32
64
>64
MIC (mg/L)
CTB-AVI
CTB
CZA




**Keyword 1**
Antimicrobial resistance (AMR)
**Keyword 2**
Antimicrobial susceptibility testing (AST)
**Keyword 3 (Please provide your suggestion)**
Ceftibuten