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A novel method to evaluate ceftazidime/avibactam therapy in patients with carbapenemase-producing Enterobacteriaceae (CPE) bloodstream infections

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Gatti, M., Tam, V.H., Gaibani, P., Cojutti, P.G., Viale, P., Pea, F. (2023). A novel method to evaluate ceftazidime/avibactam therapy in patients with carbapenemase-producing Enterobacteriaceae (CPE) bloodstream infections. INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, 61(4), 1-3 [10.1016/j.ijantimicag.2023.106760].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/931160> since: 2023-06-15

*Published:*

DOI: <http://doi.org/10.1016/j.ijantimicag.2023.106760>

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1 **A novel method to evaluate ceftazidime/avibactam therapy in patients with carbapenemase-producing**  
2 **Enterobacteriaceae (CPE) bloodstream infections**

3

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22

23 **Abstract**

24 We report our experience managing 8 patients with bloodstream infections treated with ceftazidime-  
25 avibactam continuous infusion. By adopting the innovative concept of effective MIC with an inhibitor  
26 ( $MIC_i$ ), we found a trend towards higher microbiological failure and resistance development in patients with  
27 lower ceftazidime  $fC_{ss}/MIC_i$  ratio (2/3 vs 0/5). Assessment of changes in ceftazidime MIC in relation to  
28 increasing avibactam concentration could represent a more robust PK/PD method in predicting  
29 microbiological failure given beta-lactam/beta-lactamase inhibitor combinations.

30

31 **Keywords:** continuous infusion ceftazidime-avibactam; CPE BSIs; effective MIC with an inhibitor;  
32 microbiological eradication; resistance development

33

## 34 **Introduction**

35           The widespread of carbapenemase-producing *Enterobacteriales* (CPE) is a worrisome health concern,  
36 and represents one of the main causes of hospital morbidity and mortality worldwide [1]. Among the recently  
37 licensed novel beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, ceftazidime/avibactam (CAZ-  
38 AVI) showed promising *in vitro* and *in vivo* activity against either KPC and OXA-48-like-producing  
39 *Enterobacteriales* [2]. However, the non-negligible occurrence of resistance development with CAZ-AVI  
40 therapy currently represents a remarkable concern [3]. Different strategies could be helpful in dealing with  
41 the resistance development risk. Administration by continuous infusion (CI) could represent a valuable  
42 approach for attaining optimal exposures of CAZ-AVI [4]. Additionally, a recent preclinical model showed  
43 that increasing avibactam concentrations may result in lowering of ceftazidime minimum inhibitory  
44 concentration (MIC) against KPC isolates [5]. This latter finding made possible the adoption of the  
45 innovative concept of effective MIC with an inhibitor (previously termed MIC<sub>i</sub>) as a powerful strategy for  
46 assessing the PK/PD targets of BL/BLIs [5]. The aim of this pilot study was to assess the potential role that  
47 this novel way of assessing the PK/PD of CAZ-AVI in predicting microbiological outcome in a case series of  
48 patients with documented CPE bloodstream infections (BSIs) who underwent CAZ-AVI therapeutic drug  
49 monitoring (TDM).

50

## 51 **Methods**

52           Patients who were treated with CI CAZ-AVI for documented CPE BSIs and who underwent real-  
53 time therapeutic drug monitoring (TDM) at the IRCCS Azienda Ospedaliero-Universitaria of Bologna in the  
54 period 01<sup>st</sup> September 2021-30<sup>th</sup> September 2022 were retrospectively included. Demographics and  
55 clinical/microbiological data were retrieved for each patient.

56           CAZ-AVI was started with a loading dose of 2.5 g over 2-h followed by a maintenance dose (MD)  
57 of 2.5 g q8h over 8h (namely by CI). Subsequent MD dosing adjustments were TDM-guided, as previously  
58 described [4]. Blood samples for measuring ceftazidime and avibactam steady-state concentrations (C<sub>ss</sub>) were  
59 collected firstly within 72 hours. Total ceftazidime and avibactam serum concentrations were determined by  
60 means of a validated liquid chromatography-tandem mass spectrometry method [6].

61 Antimicrobial susceptibility testing on CPE collected from patients included in this study was  
62 performed by broth microdilution (Merlin Diagnostika GMBH, Bornheim-Hersel, Germany) and MICs for  
63 CAZ-AVI were confirmed by MIC-test-strips (Liofilchem, Roseto degli Abruzzi, Italy). Carbapenemase  
64 production was assessed by lateral flow immunoassay (LFIA) and confirmed by molecular analysis, as  
65 previously described [7]. MIC results were interpreted following EUCAST clinical breakpoints v.12.0  
66 ([https://www.eucast.org/clinical\\_breakpoints/](https://www.eucast.org/clinical_breakpoints/)).

67 Additionally, ceftazidime susceptibility was tested in the presence of increasing avibactam  
68 concentrations by means of broth microdilution method. Briefly, each plate was inoculated with increasing  
69 avibactam concentrations ranging from 1 to 64 mg/L, and supplemented with serial dilution of ceftazidime  
70 ranging from 1 to 512 mg/L. The MIC of ceftazidime was determined as the lowest concentration inhibiting  
71 bacterial growth in presence of avibactam. An inhibitory sigmoid  $E_{max}$  model was used to describe  
72 ceftazidime MIC reduction as a function of increasing avibactam concentrations. Subsequently, the  $MIC_i$  was  
73 derived by conditioning the best-fit model using avibactam  $C_{ss}$ , as previously described [5]. Assuming 10%  
74 plasma protein binding [8], ceftazidime  $fC_{ss}/MIC_i$  ratio was calculated for each patient and correlated to  
75 microbiological outcomes. Microbiological eradication was defined as the absence of the index pathogen in  
76 at least two subsequent assessment of blood cultures collected at least 48h after starting treatment [3].  
77 Resistance development was defined as a CAZ-AVI MIC increase beyond the EUCAST clinical breakpoint  
78 of susceptibility.

79 Continuous data were presented as the mean  $\pm$  standard deviation (S.D.) or median and interquartile  
80 range (IQR), whereas categorical variables were expressed by count and percentage. Fisher's exact test was  
81 used for comparing the relationship between  $fC_{ss}/MIC_i$  ratio and microbiological outcome. A  $p$  value  $<0.05$   
82 was considered statistically significant.

83

## 84 **Results**

85 Eight patients (mean age  $58.9 \pm 15.6$  years; male 50%) with CPE BSIs were included. Demographics  
86 and clinical/microbiological characteristics are shown in **Table 1**. CPE isolated from blood cultures were  
87 KPC-producing *Klebsiella pneumoniae*, OXA-181 producing *Klebsiella pneumoniae*, and OXA-181  
88 producing *Escherichia coli* in four, three, and one patient, respectively. Of note, one *Klebsiella pneumoniae*

89 strain was both KPC and OXA-181 carbapenemases co-producer. BSIs were primary in two cases and  
90 secondary to deep-seated infections in the other six (four intrabdominal infections and two ventilator-  
91 acquired pneumonia). All but one patients were treated with CAZ-AVI monotherapy. Source control was  
92 deemed (partially or completely) adequate in 3 out of 4 cases of BSI attributed to intra-abdominal sources.

93 All CPE isolates were susceptible to CAZ-AVI, but had different magnitudes of ceftazidime MIC  
94 reduction when exposed to increasing avibactam concentrations (i.e., ranging from 5- to 8-log). The MIC<sub>i</sub>  
95 was lower than the ceftazidime  $fC_{ss}$  in all cases. Microbiological eradication occurred in six out of eight  
96 cases (75%). Microbiological failure and CAZ-AVI resistance development at follow-up blood cultures  
97 occurred in two cases (25%). Patients with lower  $fC_{ss}/MIC_i$  ratios had a trend toward higher microbiological  
98 failure and resistance development to CAZ-AVI (2/3 vs 0/5; p=0.11).

99

## 100 Discussion

101 We applied a novel method to evaluate CAZ-AVI therapy in patients with CPE BSI. Interestingly,  
102 the findings suggested that escalating avibactam concentrations resulted in variable ceftazidime MIC  
103 decrease in CPE isolates producing KPC or OXA-48-like carbapenemase. Previous preclinical and clinical  
104 evidence have clearly established which are the optimal PK/PD targets for maximizing  
105 clinical/microbiological efficacy of beta-lactams and resistance suppression against Gram-negative isolates  
106 [9,10]. However, optimal dosing strategy still remains an unexplored field for BL/BLIs [11]. It is worth  
107 noting that patients having microbiological failure were those with CPE isolates exposed to the lower  
108 avibactam  $C_{ss}$  during treatment and having less pronounced ceftazidime MIC reduction.

109 Our innovative approach may represent a paradigm shift in assessing therapy with BL/BLIs.  
110 Interestingly, the MIC<sub>i</sub> may represent a dynamic way for identifying the ceftazidime MIC changes in relation  
111 to avibactam concentration increase, and the potential impact that this approach may have on microbiological  
112 eradication. Notably, this novel way could provide a more informative PK/PD tool compared to the  
113 traditional one that is based on the achievement of a fixed concentration BLI. Our findings were consistent  
114 with previous findings showing that the MIC<sub>i</sub> concept could be used to guide dosing of piperacillin-  
115 tazobactam against ESBL-producing *Enterobacterales* and with CAZ-AVI against KPC-producing  
116 *Enterobacterales* [5,12]. Consequently, the concept could represent a helpful tool to establish TDM-

117 measured PK/PD targets of other novel BL/BLIs (e.g., meropenem-vaborbactam, imipenem-relebactam) in  
118 real-world scenario.

119 The limited sample size prevents us from drawing any robust conclusion on the absolute PK/PD  
120 target. Other limitations include the lack of quantitative bacterial burden and heteroresistance evaluations.  
121 However, our proof-of-concept findings demonstrated a promising trend to evaluate CAZ-AVI therapy in  
122 patients affected by CPE infections. In contrast to conventional susceptibility testing, more robust PK/PD  
123 analysis could be provided by assessing avibactam concentration-dependent changes in ceftazidime MIC.  
124 Larger studies are warranted to confirm our hypothesis before this approach would be routinely applied  
125 within a diagnostic laboratory.

126

127

## 128 **Declarations**

129 **Funding:** This study is supported in part by the National Institutes of Health (R01AI140287-05 to VHT).

130 **Competing Interests:** M.G. reports grants from Angelini S.p.A., outside the submitted work; V.H.T. has  
131 received consultant fees from Taxis Pharmaceuticals, Inc. outside the submitted work;; F.P. has participated  
132 in speaker's bureau for Angelini, BeiGene, Gilead, Menarini, MSD, Pfizer, Sanofi-Aventis, Shionogi, and as  
133 consultant for Angelini, bioMérieux, BeiGene, Gilead, MSD, Pfizer, Shionogi, outside the submitted work;  
134 P.V. has served as a consultant for bioMérieux, Gilead, Merck Sharp & Dohme, Nabriva, Nordic Pharma,  
135 Pfizer, Thermo-Fisher, and Venatorx, and received payment for serving on the speaker's bureaux for  
136 Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma, and Pfizer, outside the submitted work. The other  
137 authors report no potential conflicts of interest for this work.

138 **Ethical Approval:** The study was conducted according to the guidelines of the Declaration of Helsinki and  
139 approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (n.  
140 442/2021/Oss/AOUBo approved on 28th June 2021).

141 **Sequence Information:** Not applicable

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184

185 **Table 1** – Demographics and clinical features of patients with bloodstream infections due to carbapenemase-producing *Enterobacteriales* treated with continuous  
 186 infusion ceftazidime-avibactam

ID case	Age/Sex	Species	Carbapenemase	Susceptibility (mg/L)			Source of BSI	Combination therapy	Ceftazidime average <i>f</i> C <sub>ss</sub>	Avibactam average C <sub>ss</sub>	Ceftazidime <i>f</i> C <sub>ss</sub> /MIC <sub>i</sub> ratio	Microbiological eradication	Resistance development
				MER	CAZ	CAZ-AVI*							
#1	75/M	<i>K. pneumoniae</i>	KPC	≥64	256	4	IAI	No	110.7	30.1	1278	Yes	No
#2	41/F	<i>K. pneumoniae</i>	KPC	16	256	1	VAP	No	74.3	30.9	1280	Yes	No
#3	87/F	<i>E. coli</i>	OXA-181	1	>256	2	IAI	No	60.6	15.1	445	Yes	No
#4	55/M	<i>K. pneumoniae</i>	OXA-181	1	32	0.5	IAI	No	34.8	8.2	191	Yes	No
#5	45/M	<i>K. pneumoniae</i>	KPC	>32	>256	4	primary	No	12.6	3.7	9	Yes	No
#6	64/M	<i>K. pneumoniae</i>	OXA-181	32	64	2	VAP	Fosfomycin	42.6	18.3	47	No	Yes (MIC 64 mg/L)
#7	63/F	<i>K. pneumoniae</i>	KPC and OXA-181 <sup>§</sup>	>64	>256	8	primary	No	58.5	18.0	259	Yes	No
#8	41/F	<i>K. pneumoniae</i>	KPC	>64	>256	8	IAI	No	24.7	5.8	17	No	Yes (MIC 32 mg/L)

187

188 BSI: bloodstream infection; CAZ-AVI: ceftazidime/avibactam; CAZ: ceftazidime *f*C<sub>ss</sub>: free steady-state concentration; IAI: intrabdominal infection; *pneumoniae*; MER: meropenem; MIC: minimum  
 189 inhibitory concentration; VAP: ventilator-associated pneumonia

190 \* at fixed concentration of avibactam 4 mg/L

191 § Co-production of KPC and OXA-181 carbapenemases