

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

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>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

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

3

4 Milo Gatti^{1,2}, Vincent H. Tam^{3*}, Paolo Gaibani⁴, Pier Giorgio Cojutti^{1,2}, Pierluigi Viale^{1,5}, Federico
5 Pea^{1,3}

6

7 ¹ Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna,
8 Italy

9 ² Clinical Pharmacology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

10 ³ Department of Pharmacy Practice and Translational Research, University of Houston College of Pharmacy,
11 Houston, Texas, USA

12 ⁴ Division of Microbiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

13 ⁵ Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

14

15

16 Corresponding author: Vincent H. Tam

17 Department of Pharmacy Practice and Translational Research

18 University of Houston College of Pharmacy

19 4349 Martin Luther King Boulevard, Houston, TX 77204, USA

20 Phone: 1 (832) 842-8316; Fax: 1 (832) 842-8383; E-mail: vtam@uh.edu

21

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 *Enterobacterales* (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 *Enterobacterales* [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_i) 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).

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 01st September 2021-30th 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_{ss}) 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].

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

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

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

Results

Eight patients (mean age 58.9 ± 15.6 years; male 50%) with CPE BSIs were included. Demographics and clinical/microbiological characteristics are shown in **Table 1**. CPE isolated from blood cultures were KPC-producing *Klebsiella pneumoniae*, OXA-181 producing *Klebsiella pneumoniae*, and OXA-181 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_i
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_i 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_i 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 Correio, 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

142 **References**

- 143 [1] Taconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research,
144 and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and
145 tuberculosis. *Lancet Infect Dis* 2018;18:318–27. [https://doi.org/10.1016/S1473-3099\(17\)30753-3](https://doi.org/10.1016/S1473-3099(17)30753-3).
- 146 [2] Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β -Lactam- β -Lactamase
147 Inhibitor Combinations. *Clin Microbiol Rev* 2020;34. <https://doi.org/10.1128/CMR.00115-20>.
- 148 [3] Shields RK, Nguyen MH, Chen L, Press EG, Kreiswirth BN, Clancy CJ. Pneumonia and Renal
149 Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance
150 among Patients with Carbapenem-Resistant Enterobacteriaceae Infections. *Antimicrob Agents*
151 *Chemother* 2018;62. <https://doi.org/10.1128/AAC.02497-17>.
- 152 [4] Gatti M, Pascale R, Cojutti PG, Rinaldi M, Ambretti S, Conti M, et al. A descriptive
153 pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime/avibactam in a case
154 series of renal critically ill patients treated for documented carbapenem-resistant Gram-negative
155 bloodstream infections and/or ventilator-associated pneumonia. *International Journal of Antimicrobial*
156 *Agents* 2022;106699. <https://doi.org/10.1016/j.ijantimicag.2022.106699>.
- 157 [5] Tam VH, Merlau PR, Hudson CS, Kline EG, Eales BM, Smith J, et al. Optimal ceftazidime/avibactam
158 dosing exposure against KPC-producing *Klebsiella pneumoniae*. *J Antimicrob Chemother*
159 2022;77:3130–7. <https://doi.org/10.1093/jac/dkac294>.
- 160 [6] Sillén H, Mitchell R, Sleigh R, Mainwaring G, Catton K, Houghton R, et al. Determination of
161 avibactam and ceftazidime in human plasma samples by LC-MS. *Bioanalysis* 2015;7:1423–34.
162 <https://doi.org/10.4155/bio.15.76>.
- 163 [7] Gaibani P, Bovo F, Bussini L, Lazzarotto T, Amadesi S, Bartoletti M, et al. Dynamic evolution of
164 imipenem/relebactam resistance in a KPC-producing *Klebsiella pneumoniae* from a single patient
165 during ceftazidime/avibactam-based treatments. *J Antimicrob Chemother* 2022;77:1570–7.
166 <https://doi.org/10.1093/jac/dkac100>.
- 167 [8] Merdjan H, Rangaraju M, Tarral A. Safety and pharmacokinetics of single and multiple ascending
168 doses of avibactam alone and in combination with ceftazidime in healthy male volunteers: results of

two randomized, placebo-controlled studies. Clin Drug Investig 2015;35:307–17.
<https://doi.org/10.1007/s40261-015-0283-9>.

[9] Tam VH, Chang K-T, Zhou J, Ledesma KR, Phe K, Gao S, et al. Determining β -lactam exposure threshold to suppress resistance development in Gram-negative bacteria. J Antimicrob Chemother 2017;72:1421–8. <https://doi.org/10.1093/jac/dkx001>.

[10] Gatti M, Cojutti PG, Pascale R, Tonetti T, Laici C, Dell’Olio A, et al. Assessment of a PK/PD Target of Continuous Infusion Beta-Lactams Useful for Preventing Microbiological Failure and/or Resistance Development in Critically Ill Patients Affected by Documented Gram-Negative Infections. Antibiotics 2021;10:1311. <https://doi.org/10.3390/antibiotics10111311>.

[11] Crass RL, Pai MP. Pharmacokinetics and Pharmacodynamics of β -Lactamase Inhibitors. Pharmacotherapy 2019;39:182–95. <https://doi.org/10.1002/phar.2210>.

[12] Tam VH, Abodakpi H, Wang W, Ledesma KR, Merlau PR, Chan K, et al. Optimizing pharmacokinetics/pharmacodynamics of β -lactam/ β -lactamase inhibitor combinations against high inocula of ESBL-producing bacteria. J Antimicrob Chemother 2021;76:179–83. <https://doi.org/10.1093/jac/dkaa412>.

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

ID case	Age/Sex	Species	Carbapenemase	Susceptibility (mg/L)			Source of BSI	Combination therapy	Ceftazidime average fC_{ss}	Avibactam average C_{ss}	Ceftazidime fC_{ss}/MIC_i 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 [§]	>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 fC_{ss} : 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