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

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Abstract

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

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

Introduction

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

Methods

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

CAZ-AVI was started with a loading dose of 2.5 g over 2-h followed by a maintenance dose (MD) of 2.5 g q8h over 8h (namely by CI). Subsequent MD dosing adjustments were TDM-guided, as previously described [4]. Blood samples for measuring ceftazidime and avibactam steady-state concentrations (C_{ss}) were collected firstly within 72 hours. Total ceftazidime and avibactam serum concentrations were determined by 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 ± 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*

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

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

Discussion

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

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

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

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

Declarations

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

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

Sequence Information: Not applicable

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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 *f*Css	Avibactam average Css	Ceftazidime *f*Css/MIC$_i$ ratio	Microbiolgical eradication	Resistance development
				MER	CAZ	CAZ-AVI*							
#1	75/M	*K. pneumoniae*	KPC	>=64	256	4	IAI	No	110.7	30.1	1278	Yes	No
#2	41/F	*K. pneumoniae*	KPC	16	256	1	VAP	No	74.3	30.9	1280	Yes	No
#3	87/F	*E. coli*	OXA-181	1	>256	2	IAI	No	60.6	15.1	445	Yes	No
#4	55/M	*K. pneumoniae*	OXA-181	1	32	0.5	IAI	No	34.8	8.2	191	Yes	No
#5	45/M	*K. pneumoniae*	KPC	>32	>256	4	primary	No	12.6	3.7	9	Yes	No
#6	64/M	*K. pneumoniae*	OXA-181	32	64	2	VAP	Fosfomycin	42.6	18.3	47	**No**	**Yes (MIC 64 mg/L)**
#7	63/F	*K. pneumoniae*	KPC and OXA-181§	>64	>256	8	primary	No	58.5	18.0	259	Yes	No
#8	41/F	*K. pneumoniae*	KPC	>64	>256	8	IAI	No	24.7	5.8	17	**No**	**Yes (MIC 32 mg/L)**

BSI: bloodstream infection; CAZ-AVI: ceftazidime/avibactam; CAZ: ceftazidime *f*C$_{ss}$: free steady-state concentration; IAI: intrabdominal infection; *pneumoniae*; MER: meropenem; MIC: minimum inhibitory concentration; VAP: ventilator-associated pneumonia

* at fixed concentration of avibactam 4 mg/L

§ Co-production of KPC and OXA-181 carbapenemases