A descriptive pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime-avibactam in a case series of critically ill renal patients treated for documented carbapenem-resistant Gram-negative bloodstream infections and/or ventilator-associated pneumonia

A descriptive pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime/avibactam in a case series of renal critically ill patients treated for documented carbapenem-resistant Gram-negative bloodstream infections and/or ventilator-associated pneumonia

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Abstract

Objectives: To describe the pharmacokinetic/pharmacodynamic (PK/PD) behaviour of continuous infusion (CI) ceftazidime/avibactam and the microbiological outcome in a case series of renal critically ill patients treated for documented carbapenem-resistant Gram-negative (CR-GN) bloodstream infections (BSI) and/or ventilator-associated pneumonia (VAP).

Methods: Critically ill patients with different degrees of renal function treated with CI ceftazidime-avibactam for documented CR-GN infections and underwent therapeutic drug monitoring from April 2021 to March 2022 were retrospectively assessed. Ceftazidime and avibactam concentrations were determined at steady-state, and the free fraction (fC_{ss}) was calculated. The joint PK/PD target of ceftazidime-avibactam was considered as optimal when both C_{ss}/MIC ratio for ceftazidime≥4 (equivalent to 100%$fT_{>4xMIC}$) and C_{ss}/C_T ratio for avibactam>1 (equivalent to 100% $fT>C_T$ of 4.0 mg/L) were simultaneously achieved (quasi-optimal if only one of the two was achieved, and suboptimal if none of the two was achieved). Relationship between ceftazidime-avibactam PK/PD targets and microbiological outcome was assessed.

Results: Ten patients with documented CR-GN infections (5 BSIs, 4 VAP, and one BSI+VAP) were retrieved. The joint PK/PD targets of ceftazidime-avibactam were optimal and quasi-optimal in 8 and 2 cases, respectively. Microbiological failure occurred in two patients (one with VAP and the other with BSI+VAP), and one of these developed ceftazidime-avibactam resistance. Both underwent renal replacement therapy, and failed despite attaining optimal joint PK/PD target and receiving fosfomycin co-treatment.

Conclusion: CI administration may allow the attainment of optimal joint PK/PD targets of ceftazidime-avibactam in most critical renal patients with CR-GN infections, and may be helpful in minimizing the risk of microbiological failure.

Keywords: ceftazidime-avibactam; continuous infusion; carbapenem-resistant Gram-negative infections; PK/PD target attainment; critical renal patients; microbiological failure

Background

The widespread diffusion of difficult-to-treat resistant (DTR) Gram-negative pathogens is a worrisome health concern, and represents one of the main causes of hospital morbidity and mortality [1]. Several novel beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations have been recently licensed for the management of carbapenem-resistant *Enterobacterales* (CRE) and/or carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA) infections [2].

Ceftazidime-avibactam is a novel BL/BLI combination with *in vitro* and *in vivo* activity against either *Klebsiella pneumoniae* carbapenemase (KPC)-producing and OXA-48-producing *Enterobacterales* or CR-PA [2]. Several real-world evidences have confirmed the advantages in terms of clinical outcome that ceftazidime-avibactam may have over old traditional agents in the management of DTR Gram-negative infections [3]. Preclinical models defined the joint PK/PD target for minimal efficacy of ceftazidime-avibactam (1-log kill) as the simultaneous achievement of 50% of the dose interval that free ceftazidime concentrations are above the MIC (50% *f*T>MIC) and free avibactam concentrations are greater than the threshold concentration (CT) of 1.0 mg/L (50% *f*T > CT of 1.0 mg/L) [4,5].

However, recent findings suggested that minimum PK/PD targets of beta-lactams may not be adequate when treating severe Gram-negative deep-seated infections in the critically ill patients. More aggressive PK/PD targets up to 100% $T_{>4\text{-}8\ x\ MIC}$ were shown to be helpful for maximizing clinical efficacy and microbiological eradication and for minimizing resistance development [6,7]. In this scenario, continuous infusion (CI) administration has been suggested as a valuable strategy for maximizing the achievement of optimal PK/PD targets with beta-lactams [8].

The aim of this study was to describe the pharmacokinetic/pharmacodynamic (PK/PD) behaviour of continuous infusion (CI) ceftazidime/avibactam and the microbiological outcome in a case series of critically ill patients with altered renal function who were treated with first-line or rescue therapy for documented carbapenem-resistant Gram-negative (CR-GN) bloodstream infections (BSI) and/or ventilator-associated pneumonia (VAP).

Methods

This retrospective study included a case series of critically ill patients who were treated with CI ceftazidime-avibactam for documented CRE or CR-PA infections at the intensive care units (ICUs) of the IRCCS Azienda Ospedaliero-Universitaria of Bologna between 01st April 2021 and 31st March 2022. All the included patients underwent real-time therapeutic drug monitoring (TDM) of ceftazidime-avibactam. Demographic and clinical/laboratory data were extracted for each single patient. Type/site of infection, ceftazidime-avibactam dosage, treatment duration, mono or combination therapy, MIC of ceftazidime-avibactam against CRE or CR-PA, and requirement for dosing adjustments were also collected. Combination therapy was defined as the concomitant use of other antibiotics active against the DTR Gram-negative clinical isolates.

Documented BSI was defined as the isolation of CRE from blood cultures. Documented VAP was defined as the isolation of CRE or CR-PA with a bacterial load $\geq 10^4$ CFU/mL in the bronchoalveolar lavage (BAL) fluid culture after > 48 hours from endotracheal intubation and start of mechanical ventilation [9].

Antimicrobial susceptibility of ceftazidime-avibactam was tested by broth microdilution (panel provided by Merlin Diagnostika GMBH, Bornheim-Hersel, Germany). The range of MIC values tested for ceftazidime was from 1 to 64 mg/L with a fixed target avibactam concentration (C_T) of 4 mg/L. Quality controls were performed monthly by using reference isolates provided by ATCC (namely *E. coli* 25922, *P. aeruginosa* 27853, and *K. pneumoniae* 700603). Molecular analysis of CRE isolates was performed. Carbapenemase type was determined by multiplex immunochromatographic assay NG test CARBA 5 (NG Biotech, Guipry-Messac, France) for detecting the specific carbapenemase enzyme produced (IMP, VIM, NDM, KPC, OXA-48). MIC values were interpreted according to the EUCAST guidelines [11], and resistance to ceftazidime-avibactam was defined whenever values were > 8 mg/L.

Ceftazidime-avibactam was prescribed at the discretion of the treating physician or infectious disease consultant as first-line or rescue therapy according to the current clinical practice guidelines implemented at the IRCCS Azienda Ospedaliero-Universitaria of Bologna. Treatment was always started with a loading dose (LD) of 2.5 g over 2-h infusion followed by a maintenance dose (MD) administered by CI. For this purpose, aqueous solutions were reconstituted every 8h or 12h and infused over 8-12h due to stability restrictions [10].

MD regimens were initially selected according to the patient's underlying pathophysiological conditions and renal function. To maximize the attainment of aggressive PK/PD targets, the maintenance dose of 2.5 g q8h by CI was administered to all of the patients with the intent of overcoming the major pathophysiological/iatrogenic factors that might have caused potential underexposure in the early phase of septic shock, including patients with potentially transient severe acute kidney injury. Lower maintenance dosing were implemented (i.e., 0.625-1.25 g q12h by CI) only in anuric patients who underwent intermittent haemodialysis for minimizing the risk of neurotoxicity. Higher than labeled dose (2.5 g q6h by CI) were recommended in specific clinical scenarios, namely patients affected by augmented renal clearance and/or with deep-seated infections or in patients with residual renal function undergoing high-intensity continuous renal replacement therapy.

Blood samples for measuring ceftazidime and avibactam steady-state concentrations (C_{ss}) were collected firstly within 72 hours from starting treatment and then reassessed whenever feasible. In patients requiring CVVHDF, blood samples for TDM were collected at least 24 h after starting CRRT to ensure the achievement of steady-state. Total ceftazidime and avibactam serum concentrations were determined by means of a validated liquid chromatography-tandem mass spectrometry method [12].

As only total ceftazidime and avibactam concentrations were measured, the free fraction (*f*) was calculated by considering the plasma protein binding reported in the literature (10% and 7% for ceftazidime and avibactam, respectively) [13]. The percentage of time with ceftazidime concentrations above the MIC was selected as PD parameter of ceftazidime efficacy and expressed as C_{ss}/MIC ratio. The percentage of time with avibactam concentrations above the C_T was selected as PD parameter of avibactam efficacy and expressed as C_{ss}/C_T ratio. The primary goal was the attainment of a joint PK/PD target of ceftazidime-avibactam. The joint PK/PD target of ceftazidime-avibactam was considered as optimal when both C_{ss}/MIC ratio for ceftazidime ≥ 4 (equivalent to 100% $fT_{>4 \times MIC}$) and C_{ss}/C_T ratio for avibactam > 1 (equivalent to 100% $fT > C_T$ of 4.0 mg/L) were simultaneously achieved; as quasi-optimal if only one of the two thresholds was achieved, and as suboptimal if none of the two thresholds was achieved. Ceftazidime-avibactam dosing adjustments were provided on the basis of our current clinical practice, as previously reported [14].

Microbiological failure was defined as the persistence of the same bacterial pathogen in blood culture or in BAL culture after ≥7 days from starting ceftazidime-avibactam treatment, as previously reported [15]. Resistance development was defined as the MIC increase of ceftazidime-avibactam against the clinical isolate beyond the EUCAST clinical breakpoint of susceptibility. Primary outcome was microbiological eradication, defined as the absence of the original pathogens from the blood or BAL culture of the specimens in at least two subsequent assessments. Follow-up blood cultures (in patients with BSI) and/or BAL cultures (in patients with VAP) were executed between day 2 and day 7, and between day 5 and day 14, respectively, for assessing microbiological eradication and defining treatment duration. For each patient, it was investigated the relationship between ceftazidime-avibactam PK/PD targets and microbiological outcome in relation to the site of infection (BSI and/or VAP) and to the class of renal function, which was stratified in six scenarios [intermittent haemodialysis (IHD), acute kidney injury (AKI), continuous renal replacement therapy (CRRT) in anuric patients, normal renal function, CRRT in patients with residual renal function, and augmented renal clearance (ARC)]. ARC was defined as a measured creatinine clearance ≥ 130 mL/min/1.73m^2 in males and ≥ 120 in females coupled with a normal serum creatinine value [16]. AKI was classified according to Acute Kidney Injury Network criteria, including the need for CRRT or IHD [17]. Secondary outcomes included 30-day mortality rate and occurrence of adverse events (AEs).

Descriptive statistics were used. Continuous data were presented as the mean ± standard deviation (S.D.) or median and interquartile range (IQR), whereas categorial variables were expressed by count and percentage. The study was approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (n. 442/2021/Oss/AOUBo approved on 28th June 2021).

Results

Overall, during the study period ten critically ill patients had documented CR Gram-negative BSI (n = 5) or VAP (n = 4) or BSI plus VAP (n = 1) treated with CI ceftazidime-avibactam and underwent at least one TDM assessment of ceftazidime-avibactam C_{ss} (**Table 1**). Mean (±SD) age was 60.7 ± 14.5 years with a male preponderance (70%). Seven out of 10 patients (70%) were admitted in ICU because of acute respiratory distress syndrome caused by severe COVID-19 pneumonia. The other three patients were admitted in ICU because of sepsis, which occurred after solid organ transplant (2/10) or major surgery (1/10). All patients underwent invasive mechanical ventilation, and all but one had septic shock. In regard to renal classes, six out of 10 patients (60%) underwent continuous venovenous haemodiafiltration (CVVHDF) (4 anuric and 2 with residual renal function), two (20%) underwent IHD, one each had normal renal function, AKI or ARC (10% each). One of the patients who underwent CVVHDF needed also extracorporeal membrane oxygenation (ECMO).

BSI and VAP occurred in five and four cases, respectively, whereas one patient had BSI and VAP simultaneously. All infections were microbiologically documented. Six (60%) were caused by CRE (KPC- or OXA-48-producing *Klebsiella pneumoniae* in two cases each, KPC/OXA-48 co-producing *Klebsiella pneumoniae* and AmpC-producing associated with porin loss *Klebsiella aerogenes* in one case each) and four (40%) by CR-PA. Overall, all isolates were fully susceptible to ceftazidime-avibactam, with MICs ranging from 2 to 8 mg/L.

MD of CI ceftazidime-avibactam was started at the full dosage of 2.5 g q8h over 8h in eight patients, and at the dose of 2.5 g q6h over 6h and of 0.625 g q12h over 12h in one case each. The median (IQR) duration of treatment was 13.5 days (8.25-24.75 days). Combination therapy was applied with fosfomycin in five cases and with aztreonam in another one.

Blood samples for first TDM assessment of ceftazidime-avibactam were collected on day 2 in five cases, and on day 3 in the other five. Turnaround time (TAT) of ceftazidime-avibactam was within 12 hours in 7 cases and within 48 hours in other 3 cases. The dose was confirmed in 5 out of 10 patients (50%), whereas in the other 5 cases a dose decrease was recommended. The median (IQR) average fC_{ss} of ceftazidime and avibactam were 49.9 mg/L (41.3-58.8 mg/L) and 14.1 mg/L (7.5-17.0 mg/L), respectively.

The joint PK/PD targets of ceftazidime-avibactam were optimal in eight patients (80%; 3 BSI, 4 VAP, 1 BSI + VAP), quasi-optimal in two cases (20%; 2 BSI both with avibactam $fC_{ss}/C_T < 1$), and never suboptimal. The relationships between the level of the joint PK/PD target of CI ceftazidime-avibactam and the microbiological outcome of BSI and/or VAP due to CRE and CR-PA are summarized in **Figure 1a** and **1b**, respectively. Microbiological eradication was achieved in 100% of patients with BSIs (5/5) and in 75% of those with VAPs (3/4). Microbiological failure (20%; 2/10) occurred in one patient with VAP (1/4) and in the only patient with BSI plus VAP. In this latter case, resistance of *K. pneumoniae* OXA-48-producer to ceftazidime-avibactam occurred (MIC of 64 mg/L). Both of these patients underwent renal replacement therapy and microbiologically failed despite attaining optimal joint PK/PD target of ceftazidime-avibactam and being co-treated with fosfomycin.

The overall 30-day mortality rate was 30%. None of the three patients passed away because of the CR Gram-negative infections. The underlying causes of mortality were severe COVID-19 pneumonia coupled with pulmonary invasive aspergillosis in two cases, and septic shock due to *Enterococcus faecium* in the other one. No ceftazidime/avibactam-related AEs emerged during treatment.

Discussion

To the best of our knowledge, this is the first study that described the joint PK/PD target attainment of ceftazidime-avibactam administered by CI and that assessed its relationships with the microbiological outcome in a real-world scenario of critical renal patients with documented CRE- or CR-PA- related BSI and/or VAP.

For traditional beta-lactams, administration by prolonged infusion, by achieving more aggressive PK/PD targets, was just shown to grant remarkable advantages over intermittent infusion in terms of better microbiological outcome and/or clinical outcome in critically ill patients [4,7,8].

In regard to ceftazidime-avibactam, a recent retrospective observational study assessed use and outcomes of mono- and/or combo-therapy among 577 patients with infections caused by KPC-Kp strains [18]. Interestingly, it was shown that 30-day mortality was negatively associated at multivariate regression analysis with administration by prolonged infusion (p = 0.006). These findings may suggest that prolonging infusion of ceftazidime-avibactam, by maximizing the PK/PD target attainment, may be the way forward for dealing with severe KPC-Kp infections [4,18].

Our results showed firstly that implementing a real-time TDM-guided approach of CI ceftazidime-avibactam may be helpful in attaining very aggressive joint PK/PD targets of ceftazidime-avibactam over time. Noteworthy, PK/PD target attainment was optimal in 80% of cases, and never suboptimal. This approach granted microbiological eradication in most cases both of CRE-related and of CR-PA-related BSI and/or VAP. It's worth mentioning that some real-world studies hypothesized that the unfavourable clinical outcome observed with ceftazidime-avibactam in some settings, namely pneumonia and/or during renal replacement therapy, could have been related to sub-optimal PK/PD target attainment at the infection site [15,18]. Unfortunately, none of these studies directly tested this hypothesis. Our findings, although limited, suggest that a real-time TDM-guided approach may grant the possibility of coupling optimal PK/PD target attainment with quite high microbiological eradication rates in BSI and/or VAP, and offer the opportunity to argue that this approach could be helpful in these scenarios.

To the best of our knowledge, there is only one case series that previously assessed the PK/PD target attainment of CI ceftazidime-avibactam in Outpatient Parenteral Antimicrobial Therapy (OPAT) patients, but

it did not allow to draw any reliable conclusion as it lacked measurement of avibactam concentrations [19]. It should not be overlooked that avibactam, differently from tazobactam, is a reversible beta-lactamase inhibitor [5]. This means that CI administration may be a very powerful tool in maintaining concentrations steadily over time above the safeguarded fixed threshold adopted by the EUCAST for avibactam when testing ceftazidime/avibactam susceptibility, namely 4 mg/L [11].

In our case series, the real-time TDM-guided approach was very helpful in optimizing treatment, especially because our cohort included predominantly critically ill patients with variable and fluctuating degrees of renal function. The failure rate among patients who underwent renal replacement therapy in our study was quite low compared to those observed in other previous studies (29% vs. 60-83.3%) [15,20]. This could be explained by the fact that our TDM-guided approach was focused at achieving early aggressive joint PK/PD targets of CI ceftazidime-avibactam even in renal patients [21]. Of note, we are used to start ceftazidime-avibactam therapy with full maintenance dose for ensuring aggressive joint PK/PD targets also in patients with sepsis-associated transient AKI. This approach is thought for preventing the risk of underexposure in the eventuality that renal function should recover promptly in the first 24-48h, that is before performing the first TDM assessment [22]. In this scenario, implementation of real-time TDM should be pursued for granting prompt dosing adjustments in patients with fluctuating renal function.

It should be noticed that the only two episodes of microbiological failure occurred, and concerned VAP patients. This is in agreement with previous real-world evidence showing that pneumonia may be a major risk factor of clinical failure and mortality among patients treated with ceftazidime-avibactam [15,18]. We believe that in these two patients poor underlying conditions more than inappropriate antimicrobial therapy might have played a major role in determining the negative microbiological outcome, even if we could not rule out that suboptimal PK/PD target attainment might have occurred at the infection site. One occurred in a lung transplant recipient after long ICU stay and the other in a patient with severe COVID-19 pneumonia. The occurrence of suboptimal PK/PD target in the epithelial lining fluid (ELF) seems unlikely since in both cases the joint PK/PD targets achieved in plasma were very aggressive. Considering that the ELF/plasma ratio of ceftazidime-avibactam reported in the literature is around 0.30-0.35, this approach should have ensured optimal exposure even at the infection site [23]. Development of resistance to ceftazidime-avibactam occurred

only in one case (10%), and this may support the contention that this approach could also concur in minimizing the risk of emergence of difficult-to-treat phenotypes. Notably, no death was directly attributable to antimicrobial treatment failure.

The microbiological eradication rate was very similar between patients treated with ceftazidime-avibactam in monotherapy and those receiving combination therapy, likewise reported in a recent retrospective observational study [18]. This could suggest that when aggressive joint PK/PD target of CI ceftazidime-avibactam monotherapy have been pursued, combination therapy could not offer any additional benefit.

Our study has some limitations. The retrospective monocentric study design and the limited sample size should be acknowledged. Only total ceftazidime-avibactam concentrations were measured, and the free moieties were only estimated. However, this is the first real-life experience that described the joint PK/PD target attainment of CI ceftazidime-avibactam in the treatment of severe carbapenem-resistant Gram-negative infections among critical renal patients and that explored the relationship with microbiological outcome.

In conclusion, our findings suggest that administering ceftazidime-avibactam by CI and adopting a strategy of real-time TDM-guided dosing adaptation may be very helpful in attaining very aggressive joint PK/PD targets. This approach may lead to microbiological eradication in most cases of CRE- and/or CR-PA-related BSI and/or VAP regardless of mono- or combo- therapy. Large prospective clinical studies are warranted for confirming our hypothesis.

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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).

References

[1] Marston HD, Dixon DM, Knisely JM, Palmore TN, Fauci AS. Antimicrobial Resistance. JAMA 2016;316:1193–204. https://doi.org/10.1001/jama.2016.11764.

[2] Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-Lactamase Inhibitor Combinations. Clin Microbiol Rev 2020;34. https://doi.org/10.1128/CMR.00115-20.

[3] Soriano A, Carmeli Y, Omrani AS, Moore LSP, Tawadrous M, Irani P. Ceftazidime-Avibactam for the Treatment of Serious Gram-Negative Infections with Limited Treatment Options: A Systematic Literature Review. Infect Dis Ther 2021;10:1989–2034. https://doi.org/10.1007/s40121-021-00507-6.

[4] Gatti M, Pea F. Continuous versus intermittent infusion of antibiotics in Gram-negative multidrug-resistant infections. Curr Opin Infect Dis 2021. https://doi.org/10.1097/QCO.0000000000000755.

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

[6] Guilhaumou R, Benaboud S, Bennis Y, Dahyot-Fizelier C, Dailly E, Gandia P, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation-SFAR). Crit Care 2019;23:104. https://doi.org/10.1186/s13054-019-2378-9.

[7] 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.

[8] Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis 2018;18:108–20. https://doi.org/10.1016/S1473-3099(17)30615-1.

[9] Chastre J, Fagon J-Y. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867–903. https://doi.org/10.1164/ajrccm.165.7.2105078.

[10] Ceftazidime-avibactam summary of product characteristics n.d.

[11] EUCAST - Rationale for EUCAST clinical breakpoints - Ceftazidime-avibactam 2020.

[12] Sillén H, Mitchell R, Sleigh R, Mainwaring G, Catton K, Houghton R, et al. Determination of avibactam and ceftazidime in human plasma samples by LC-MS. Bioanalysis 2015;7:1423–34. https://doi.org/10.4155/bio.15.76.

[13] Merdjan H, Rangaraju M, Tarral A. Safety and pharmacokinetics of single and multiple ascending 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.

[14] Gatti M, Cojutti PG, Bartoletti M, Tonetti T, Bianchini A, Ramirez S, et al. Expert clinical pharmacological advice may make an antimicrobial TDM program for emerging candidates more clinically useful in tailoring therapy of critically ill patients. Crit Care 2022;26:178. https://doi.org/10.1186/s13054-022-04050-9.

[15] Shields RK, Nguyen MH, Chen L, Press EG, Kreiswirth BN, Clancy CJ. Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant Enterobacteriaceae Infections. Antimicrob Agents Chemother 2018;62. https://doi.org/10.1128/AAC.02497-17.

[16] Cook AM, Hatton-Kolpek J. Augmented Renal Clearance. Pharmacotherapy 2019;39:346–54. https://doi.org/10.1002/phar.2231.

[17] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31. https://doi.org/10.1186/cc5713.

[18] Tumbarello M, Raffaelli F, Giannella M, Mantengoli E, Mularoni A, Venditti M, et al. Ceftazidime-avibactam use for KPC-Kp infections: a retrospective observational multicenter study. Clin Infect Dis 2021. https://doi.org/10.1093/cid/ciab176.

[19] Goncette V, Layios N, Descy J, Frippiat F. Continuous Infusion, Therapeutic Drug Monitoring and Outpatient Parenteral Antimicrobial Therapy with Ceftazidime-Avibactam: a Retrospective Cohort Study. J Glob Antimicrob Resist 2021. https://doi.org/10.1016/j.jgar.2021.04.015.

[20] Vena A, Giacobbe DR, Castaldo N, Cattelan A, Mussini C, Luzzati R, et al. Clinical Experience with Ceftazidime-Avibactam for the Treatment of Infections due to Multidrug-Resistant Gram-Negative Bacteria Other than Carbapenem-Resistant Enterobacterales. Antibiotics (Basel) 2020;9:E71. https://doi.org/10.3390/antibiotics9020071.

[21] Gatti M, Pea F. Pharmacokinetic/pharmacodynamic target attainment in critically ill renal patients on antimicrobial usage: focus on novel beta-lactams and beta lactams/beta-lactamase inhibitors. Expert Rev Clin Pharmacol 2021. https://doi.org/10.1080/17512433.2021.1901574.

[22] Crass RL, Rodvold KA, Mueller BA, Pai MP. Renal Dosing of Antibiotics: Are We Jumping the Gun? Clinical Infectious Diseases 2019;68:1596–602. https://doi.org/10.1093/cid/ciy790.

[23] Nicolau DP, Siew L, Armstrong J, Li J, Edeki T, Learoyd M, et al. Phase 1 study assessing the steady-state concentration of ceftazidime and avibactam in plasma and epithelial lining fluid following two dosing regimens. J Antimicrob Chemother 2015;70:2862–9. https://doi.org/10.1093/jac/dkv170.

Table 1 – Demographic and clinical features of critically ill patients with carbapenem-resistant Gram-negative infections treated with continuous infusion ceftazidime-avibactam

Age/sex	ICU admission	Type of infection and pathogen	CAZ-AVI MIC (mg/L)	CAZ-AVI dosage	CAZ-AVI treatment duration (days)	Average free ceftazidime Css (mg/L)	Average free avibactam Css (mg/L)	Ceftazidime *f*Css/MIC ratio	Avibactam *f*Css/C_T ratio	PK/PD target attainment	Dosing adjustment	Antibiotic co-treatment	CRRT ECMO CLCr	ME BSI	ME VAP	Resistance development	30-day mortality
Carbapenem-resistant Enterobacterales																	
76/F	ARDS in COVID-19	BSI CR *K. aerogenes*	2	2.5g q8h CI	9	30.8	2.6	15.4	0.6	Quasi-optimal	No	No	No CLCr 96 mL/min/1.73m^2	Yes	NA	No	No
31/M	Sepsis in OLT recipient	BSI *K. pneumoniae* KPC	2	2.5g q8h CI	15	31.5	2.4	15.8	0.6	Quasi-optimal	No	No	No ARC CLCr 133.1 mL/min/1.73m^2	Yes	NA	No	No
63/F	ARDS in COVID-19	BSI *K. pneumoniae* KPC/OXA-48	4	2.5g q8h CI	8	58.5	16.7	14.6	4.2	Optimal	No	Fosfomycin	CVVHDF Quf 2400 mL/h Anuric AKIN 3	Yes	NA	No	Yes
47/M	ARDS in COVID-19	VAP *K. pneumoniae* KPC	4	2.5g q6h CI	28	52.7	16.0	13.2	4.0	Optimal	Yes 2.5g q8h CI	No	ECMO + CVVHDF Quf 2500 mL/h Residual diuresis 715 mL/day (measured CLCr 14.1 mL/min) AKIN 3	NA	Yes	No	No
48/M	ARDS in COVID-19	VAP *K. pneumoniae* OXA-48	2	2.5g q8h CI	14	139.9	80.6	70.0	20.1	Optimal	Yes 1.25g q12h CI	Aztreonam	No CLCr 30 mL/min/1.73m^2 AKIN 2	NA	Yes	No	No
64/M	Sepsis in lung transplant recipient	BSI+VAP *K. pneumoniae* OXA-48	2	2.5g q8h CI	13	42.6	17.1	21.3	4.3	Optimal	Yes 1.25g q12h CI	Fosfomycin	CVVHDF followed by IHD Anuric AKIN 3	Yes	No	Yes (isolation of *Kp* OXA-48 with MIC = 64 mg/L on BAL 3 days after the end of treatment)	No
Carbapenem-resistant Pseudomonas aeruginosa																	
72/M	ARDS in COVID-19	BSI CR *P. aeruginosa*	4	2.5g q8h CI	43	59.0	12.2	14.8	3.0	Optimal	Yes 1.25g q8h CI	Fosfomycin	CVVDHF Quf 2806 mL/h Anuric	Yes	NA	No	No

													AKIN 3				
72/M	ARDS in COVID-19	BSI CR *P. aeruginosa*	4	2.5g q8h CI	34	78.9	18.2	19.7	4.5	Optimal	Yes 2.5g q12h CI	No	CVVHDF Quf 2505 mL/h Residual diuresis > 1000 mL/day AKIN 3	Yes	NA	No	No
73/M	Septic shock in multiple bowel resection	VAP CR – *P. aeruginosa*	2	0.625g q12h CI	8	40.9	7.3	20.5	1.8	Optimal	No	Fosfomycin	IHD Anuric AKIN 3	NA	Yes	No	Yes
61/F	ARDS in COVID-19	VAP CR – *P. aeruginosa*	8	2.5g q8h CI	7	47.3	8.4	5.9	2.1	Optimal	No	Fosfomycin	CVVHDF Quf 2700 mL/h Anuric AKIN 3	NA	No	No	Yes

AKIN: Acute Kidney Injury Network definition; ARC: augmented renal clearance; ARDS: acute respiratory distress syndrome; BAL: bronchoalveolar lavage; BSI: bloodstream infection; CAZ-AVI: ceftazidime-avibactam; CI: continuous infusion; CLCr: creatinine clearance; CR: carbapenem-resistant; C_T = target concentration of 4 mg/L; CVVHDF: continuous venovenous haemodiafiltration; ECMO: extracorporeal membrane oxygenation; IHD: intermittent haemodialysis; ME: microbiological eradication; MIC: minimum inhibitory concentration; NA: not applicable; OLT: orthotopic liver transplant; Q_{uf}: ultrafiltration rate; VAP: ventilator-associated pneumonia

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Figure Legends

Figure 1 – Description of pharmacokinetic/pharmacodynamic target attainment and microbiological outcome for ceftazidime-avibactam in patients with infections caused by carbapenem-resistant *Enterobacterales* (**Panel a**) and carbapenem-resistant *Pseudomonas aeruginosa* (**Panel b**). Green box, microbiological eradication; red box, microbiological failure; grey box, absence of the specific type of infection. Each row corresponds to a single patient. Optimal joint PK/PD targets were considered the simultaneously achievement of 100% $fT_{>4 \times MIC}$ for ceftazidime and 100% $fT > 4 \times C_T$ of 1.0 mg/L for avibactam, quasi-optimal if only one of the two thresholds was achieved, and suboptimal if none of the two thresholds was achieved. BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; PK/PD, pharmacokinetic/pharmacodynamic; VAP, ventilator-associated pneumonia.