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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

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

4

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19 **Running title:** PK/PD of CI ceftazidime/avibactam in CR-GN infections

20

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23 **Abstract**

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

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

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

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

44

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

47 **Background**

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

53 Ceftazidime-avibactam is a novel BL/BLI combination with *in vitro* and *in vivo* activity against either
54 *Klebsiella pneumoniae* carbapenemase (KPC)-producing and OXA-48-producing *Enterobacterales* or CR-PA
55 [2]. Several real-world evidences have confirmed the advantages in terms of clinical outcome that ceftazidime-
56 avibactam may have over old traditional agents in the management of DTR Gram-negative infections [3].
57 Preclinical models defined the joint PK/PD target for minimal efficacy of ceftazidime-avibactam (1-log kill)
58 as the simultaneous achievement of 50% of the dose interval that free ceftazidime concentrations are above
59 the MIC (50% $fT > MIC$) and free avibactam concentrations are greater than the threshold concentration (CT)
60 of 1.0 mg/L (50% $fT > CT$ of 1.0 mg/L) [4,5].

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

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

72 **Methods**

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

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

85 Antimicrobial susceptibility of ceftazidime-avibactam was tested by broth microdilution (panel
86 provided by Merlin Diagnostika GMBH, Bornheim-Hersel, Germany). The range of MIC values tested for
87 ceftazidime was from 1 to 64 mg/L with a fixed target avibactam concentration (C_T) of 4 mg/L. Quality controls
88 were performed monthly by using reference isolates provided by ATCC (namely *E. coli* 25922, *P. aeruginosa*
89 27853, and *K. pneumoniae* 700603). Molecular analysis of CRE isolates was performed. Carbapenemase type
90 was determined by multiplex immunochromatographic assay NG test CARBA 5 (NG Biotech, Guipry-Messac,
91 France) for detecting the specific carbapenemase enzyme produced (IMP, VIM, NDM, KPC, OXA-48). MIC
92 values were interpreted according to the EUCAST guidelines [11], and resistance to ceftazidime-avibactam
93 was defined whenever values were > 8 mg/L.

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

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

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

114 As only total ceftazidime and avibactam concentrations were measured, the free fraction (f) was
115 calculated by considering the plasma protein binding reported in the literature (10% and 7% for ceftazidime
116 and avibactam, respectively) [13]. The percentage of time with ceftazidime concentrations above the MIC was
117 selected as PD parameter of ceftazidime efficacy and expressed as C_{ss}/MIC ratio. The percentage of time with
118 avibactam concentrations above the C_T was selected as PD parameter of avibactam efficacy and expressed as
119 C_{ss}/C_T ratio. The primary goal was the attainment of a joint PK/PD target of ceftazidime-avibactam. The joint
120 PK/PD target of ceftazidime-avibactam was considered as optimal when both C_{ss}/MIC ratio for ceftazidime \geq
121 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)
122 were simultaneously achieved; as quasi-optimal if only one of the two thresholds was achieved, and as
123 suboptimal if none of the two thresholds was achieved. Ceftazidime-avibactam dosing adjustments were
124 provided on the basis of our current clinical practice, as previously reported [14].

125 Microbiological failure was defined as the persistence of the same bacterial pathogen in blood culture
126 or in BAL culture after ≥ 7 days from starting ceftazidime-avibactam treatment, as previously reported [15].
127 Resistance development was defined as the MIC increase of ceftazidime-avibactam against the clinical isolate
128 beyond the EUCAST clinical breakpoint of susceptibility. Primary outcome was microbiological eradication,
129 defined as the absence of the original pathogens from the blood or BAL culture of the specimens in at least
130 two subsequent assessments. Follow-up blood cultures (in patients with BSI) and/or BAL cultures (in patients
131 with VAP) were executed between day 2 and day 7, and between day 5 and day 14, respectively, for assessing
132 microbiological eradication and defining treatment duration. For each patient, it was investigated the
133 relationship between ceftazidime-avibactam PK/PD targets and microbiological outcome in relation to the site
134 of infection (BSI and/or VAP) and to the class of renal function, which was stratified in six scenarios
135 [intermittent haemodialysis (IHD), acute kidney injury (AKI), continuous renal replacement therapy (CRRT)
136 in anuric patients, normal renal function, CRRT in patients with residual renal function, and augmented renal
137 clearance (ARC)]. ARC was defined as a measured creatinine clearance ≥ 130 mL/min/1.73m² in males and \geq
138 120 in females coupled with a normal serum creatinine value [16]. AKI was classified according to Acute
139 Kidney Injury Network criteria, including the need for CRRT or IHD [17]. Secondary outcomes included 30-
140 day mortality rate and occurrence of adverse events (AEs).

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

145 **Results**

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

157 BSI and VAP occurred in five and four cases, respectively, whereas one patient had BSI and VAP
158 simultaneously. All infections were microbiologically documented. Six (60%) were caused by CRE (KPC- or
159 OXA-48-producing *Klebsiella pneumoniae* in two cases each, KPC/OXA-48 co-producing *Klebsiella*
160 *pneumoniae* and AmpC-producing associated with porin loss *Klebsiella aerogenes* in one case each) and four
161 (40%) by CR-PA. Overall, all isolates were fully susceptible to ceftazidime-avibactam, with MICs ranging
162 from 2 to 8 mg/L.

163 MD of CI ceftazidime-avibactam was started at the full dosage of 2.5 g q8h over 8h in eight patients,
164 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
165 of treatment was 13.5 days (8.25-24.75 days). Combination therapy was applied with fosfomycin in five cases
166 and with aztreonam in another one.

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

172 The joint PK/PD targets of ceftazidime-avibactam were optimal in eight patients (80%; 3 BSI, 4 VAP,
173 1 BSI + VAP), quasi-optimal in two cases (20%; 2 BSI both with avibactam $fC_{ss}/C_T < 1$), and never suboptimal.
174 The relationships between the level of the joint PK/PD target of CI ceftazidime-avibactam and the
175 microbiological outcome of BSI and/or VAP due to CRE and CR-PA are summarized in **Figure 1a** and **1b**,
176 respectively. Microbiological eradication was achieved in 100% of patients with BSIs (5/5) and in 75% of
177 those with VAPs (3/4). Microbiological failure (20%; 2/10) occurred in one patient with VAP (1/4) and in the
178 only patient with BSI plus VAP. In this latter case, resistance of *K. pneumoniae* OXA-48-producer to
179 ceftazidime-avibactam occurred (MIC of 64 mg/L). Both of these patients underwent renal replacement
180 therapy and microbiologically failed despite attaining optimal joint PK/PD target of ceftazidime-avibactam
181 and being co-treated with fosfomicin.

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

186 **Discussion**

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

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

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

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

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

212 it did not allow to draw any reliable conclusion as it lacked measurement of avibactam concentrations [19]. It
213 should not be overlooked that avibactam, differently from tazobactam, is a reversible beta-lactamase inhibitor
214 [5]. This means that CI administration may be a very powerful tool in maintaining concentrations steadily over
215 time above the safeguarded fixed threshold adopted by the EUCAST for avibactam when testing
216 ceftazidime/avibactam susceptibility, namely 4 mg/L [11].

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

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

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

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

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

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

256

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258

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265 report no potential conflicts of interest for this work.

266

267 **Ethical approval:** The study was conducted according to the guidelines of the Declaration of Helsinki and
268 approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (n.
269 442/2021/Oss/AOUBo approved on 28th June 2021).

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

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 fCss/MIC ratio	Avibactam fCss/C _T ratio	PK/PD target attainment	Dosing adjustment	Antibiotic co-treatment	CRRT ECMO CLCr	ME BSI	ME VAP	Resistance development	30-day mortality
76/F	ARDS in COVID-19	BSI CR <i>K. aerogenes</i>	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 <i>K. pneumoniae</i> 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 <i>K. pneumoniae</i> 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 <i>K. pneumoniae</i> 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 <i>K. pneumoniae</i> 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 <i>K. pneumoniae</i> 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 <i>Kp</i> 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 <i>P. aeruginosa</i>	4	2.5g q8h CI	43	59.0	12.2	14.8	3.0	Optimal	Yes 1.25g q8h CI	Fosfomycin	CVVDFH Quf 2806 mL/h Anuric	Yes	NA	No	No
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													AKIN 3				
72/M	ARDS in COVID-19	BSI CR – <i>P. aeruginosa</i>	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 – <i>P. aeruginosa</i>	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 – <i>P. aeruginosa</i>	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

339 **Figure Legends**

340 **Figure 1** – Description of pharmacokinetic/pharmacodynamic target attainment and microbiological outcome
341 for ceftazidime-avibactam in patients with infections caused by carbapenem-resistant *Enterobacterales* (**Panel**
342 **a**) and carbapenem-resistant *Pseudomonas aeruginosa* (**Panel b**). Green box, microbiological eradication; red
343 box, microbiological failure; grey box, absence of the specific type of infection. Each row corresponds to a
344 single patient. Optimal joint PK/PD targets were considered the simultaneously achievement of 100% $fT_{>4 \times$
345 $MIC}$ for ceftazidime and 100% $fT > 4 \times C_T$ of 1.0 mg/L for avibactam, quasi-optimal if only one of the two
346 thresholds was achieved, and suboptimal if none of the two thresholds was achieved. BSI, bloodstream
347 infection; CAZ-AVI, ceftazidime-avibactam; PK/PD, pharmacokinetic/pharmacodynamic; VAP, ventilator-
348 associated pneumonia.