RESEARCH ARTICLE

Beta-lactam dosing during continuous renal replacement therapy: a survey of practices in French intensive care units

Elodie Matusik1,2*, Justine Lemtiri2, Guillaume Wabont1 and Fabien Lambiotte2

Abstract

Background: Little information is available on current practice in beta-lactam dosing during continuous renal replacement therapy (CRRT). Optimized dosing is essential for improving outcomes, and there is no consensus on the appropriate dose regimens. The objective of the present study was to describe current practice for beta-lactam dosing during CRRT in intensive care units (ICUs).

Methods: We conducted a nationwide survey by e-mailing an online questionnaire to physicians working in ICUs in France. The questionnaire included three sections: demographic characteristics, CRRT practices, and beta-lactam dosing regimens during CRRT.

Results: 157 intensivists completed the questionnaire. Continuous venovenous hemofiltration was the most frequently used CRRT technique, and citrate was the most regularly used anticoagulant. The median prescribed dose at baseline was 30 mL/kg/h. The majority of prescribers (57%) did not reduce beta-lactam dosing during CRRT. The tools were used to adapt dosing regimens during CRRT included guidelines, therapeutic drug monitoring (TDM), and data from the literature. When TDM was used, 100% T > 4 time the MIC was the most common mentioned pharmacokinetic/pharmacodynamic target (53%). Pharmacokinetic software tools were rarely used. Prolonged or continuous infusions were widely used during CRRT (88%). Institutional guidelines on beta-lactam dosing during CRRT were rare. 41% of physicians sometimes consulted another specialist before adapting the dose of antibiotic during CRRT.

Conclusions: Our present results highlight the wide range of beta-lactam dosing practices adopted during CRRT. Personalized TDM and the implementation of Bayesian software appear to be essential for optimizing beta-lactam dosing regimens and improving patient outcomes.

Keywords: Beta-lactams, Pharmacokinetics, Renal replacement therapy, Critical illness, Surveys and questionnaires

Background

Beta-lactams are the most widely prescribed antibiotics in critically ill patients. Optimized dosing of beta-lactams is required to deal with pharmacokinetic changes and frequent underdosing – especially during the early phase of sepsis [1–3]. Renal failure may protect patients from insufficient antibiotic exposure by increasing the probability of beta-lactam target concentration attainment [2–5], and patients may benefit from high doses – particularly during the first 24 to 48 h of antibiotic treatment [3, 6]. Several experts have called for caution when using reduced dosing regimens in patients receiving continuous renal replacement therapy (CRRT) [7, 8]. Seyler et al. demonstrated the inadequacy of the recommended beta-lactam dosing regimens during CRRT when bacteria with a high

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minimal inhibitory concentration (MIC) are involved
[9]. Underdosing has prompted several experts to sug-
gest the use of non-adjusted dosing within the first 24
to 48 h [10–14], albeit with a potential risk of overdose
[12–15]. Although beta-lactam dosing can be guided by
clinical and pharmacokinetic data from the literature,
the studies concern mainly intermittent hemodialysis
and cannot be applied to CRRT, for which a variety of
practices are used [15, 16]. Li and Vaara highlighted
the lack of key information required to correctly inter-
pret studies and devise dose adjustments [18, 19]. In
2019, these marked differences in CRRT practices and
the subsequent influence on beta-lactam elimination
prompted two French learned societies to recommend
therapeutic drug monitoring (TDM) of beta-lactams in
patients receiving CRRT [5]. In 2020, several inter-
national learned societies recommended TDM for routine
use in critically ill patients [20]. However, TDM is not
often available outside university hospitals. Given these
uncertainties and our experience that neurotoxicity is
more frequent in patients receiving CRRT, we decided
to survey beta-lactam dosing practices during CRRT in
France.

Methods
Survey development
Given the absence of data on the beta-lactam dosing pre-
scribed during CRRT in France, we designed a survey to
assess current practices. It was developed by a pharmacy
resident with help from a critically ill clinical pharmacist
and an intensivist, after a review of the literature. We
performed an online, nationwide, cross-sectional survey
between July and September 2019 by emailing a ques-
tionnaire to 1423 senior physicians working in intensive
care units (ICUs) across France. The survey included
22 questions on the respondents’ characteristics, CRRT
practices, and beta-lactam dosing regimens during
CRRT. The English version of the questionnaire and the
results are given in Table 1. In order to determine which
membrane material was used, brand names were cited
in the questionnaire. Three clinical vignettes describing
a critically ill patient weighing 70 kg and being treated
for infectious pneumonia with piperacillin-tazobactam,
cefotaxime or meropenem were used to prompt respond-
ents to describe their beta-lactam dosing practices dur-
ing CRRT (at 25 ml/kg/h). The questionnaire was made
available on Google Forms® (Google, Inc., Mountain
View, CA, USA). Data were extracted into an Excel®
spreadsheet (Microsoft Corp, Redmond, WA, USA). Par-
ticipation was anonymous. According to French legisla-
tion, approval by an investigational review board was not
required for this survey.

Statistical analysis
The results were presented as the frequency (percent-
age) for qualitative variables and the median [interquar-
tile range (IQR)] for quantitative variables. For statistical
comparisons of different groups, we applied Pearson's
chi-square test with Yates’ correction. All tests were two-
sided, and the threshold for statistical significance was
set to p<0.05. Statistical tests were performed using SAS®
software (version 3.8, SAS Institute, Cary, NC, USA).

Results
The respondents’ characteristics
Of the 1423 physicians contacted, 157 (11%) replied.
Physicians working in university hospitals accounted for
50% of the respondents, whereas 45% of the respondents
worked in public-sector general hospitals and 5% worked
in private for-profit or non-profit hospitals. They had a
median of 10 years [4–18] of experience in the ICU. Most
of the physicians had trained in critical care medicine
(49%) and anesthesiology (39%).

CRRT practices
Concerning renal replacement therapy (RRT), CRRT
was preferred to intermittent hemodialysis (70%). The
CRRT techniques used by intensivists were variously
venovenous hemofiltration (73%), venovenous hemo-
dialfiltration (57%), venovenous hemodialysis (55%), and
Sustained Low-Efficiency Dialysis (8%). Half of the physi-
cians (52%) reported prescribing continuous venovenous
hemofiltration preferentially, followed by continuous
venovenous hemodialysis (35%). 64% of the respondents
used citrate as the anticoagulant. 77% of the physicians
prescribing hemofiltration reported using a combined
predilution and postdilution modality. The median pre-
scribed dose at initiation was 30 mL/kg/h, and 75% of
the prescribers considered the total body weight (with
39% for body weight on admission and 36% for body
weight on the day of the CRRT prescription). 12% of the
respondents reported prescribing a flow effluent irre-
spective of body weight. Polycrylonitrile was the most
commonly used membrane material (61%, 40% of which
were polyethylenimine-coated), followed by polysulfone
(39%).

Beta-lactam dosing regimens during CRRT
Concerning beta-lactam prescriptions during CRRT,
the majority of the physicians (56%) did not adjust the
doses. 17% and 9% of them prescribed full doses for 24
and 48 h, respectively, before reducing the dosing regi-
mens. 13% of respondents reported prescribing a single
loading dose before dose adjustment and 4% reported
that their use of a reduced dose or a full dose depended

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### Table 1  The survey results

| Questions                                                                 | Responses are n/N (%) unless otherwise indicated |
|---------------------------------------------------------------------------|-------------------------------------------------|
| **Demographic characteristics**                                           |                                                 |
| What is your medical qualification?                                       |                                                 |
| Critical care medicine                                                   | 77/157 (49)                                    |
| Anesthesiology                                                           | 61/157 (39)                                    |
| Pulmonology                                                               | 5/157 (3)                                      |
| Nephrology                                                                | 5/157 (3)                                      |
| Emergency                                                                 | 4/157 (3)                                      |
| Internal medicine                                                         | 2/157 (1)                                      |
| Cardiology                                                                | 2/157 (1)                                      |
| Infectious disease                                                       | 1/157 (1)                                      | For how many years have you worked in an ICU (years, median [IQR]) | 10 [4-18] |
| In which type of institution do you work?                                 |                                                 |
| University hospital                                                       | 78/157 (50)                                    |
| Public-sector general hospital                                            | 71/157 (45)                                    |
| Private-sector for-profit or non-profit hospital                          | 8/157 (5)                                      |
| **CRRT practices**                                                       |                                                 |
| Which RRT modality do you most commonly use?                             | 110/157 (70)                                   |
| Continuous renal replacement therapy                                      | 47/157 (30)                                    |
| Intermittent renal replacement therapy                                    |                                                 |
| Which CRRT techniques do you use?                                        | 114/157 (71)                                   |
| Continuous venovenous hemofiltration                                     | 89/157 (57)                                    |
| Continuous venovenous hemodialysis                                       | 87/157 (55)                                    |
| Sustained Low-Efficiency Dialysis                                        | 13/157 (8)                                     |
| Which is the most commonly used CRRT technique?                          | 81/156 (52)                                    |
| Continuous venovenous hemofiltration                                     | 54/156 (35)                                    |
| Continuous venovenous hemodialysis                                       | 21/156 (13)                                    |
| Which is the most commonly used anticoagulant?                           | 100/157 (64)                                   |
| Citrate                                                                   | 57/157 (36)                                    |
| Heparin                                                                   |                                                 |
| If you use continuous venovenous hemofiltration or hemodiafiltration, which hemofiltration mode do you prefer? | 22/142 (16)                                    |
| Postdilution mode                                                        | 11/142 (8)                                     |
| Predilution mode                                                         | 106/142 (77)                                   |
| Pre/postdilution mode                                                    |                                                 |
| Which is the most commonly used CRRT dose, and how do you adjust it?     | 9/157 (6)                                      |
| 20 mL/kg/h                                                                | 36/157 (23)                                    |
| 25 mL/kg/h                                                                | 49/157 (31)                                    |
| 30 mL/kg/h                                                                | 45/157 (29)                                    |
| 35 mL/kg/h                                                                | 12/157 (8)                                     |
| 2000 mL/h (effluent flow not adjusted for body weight)                   | 3/157 (2)                                      |
| 2500 mL/h (effluent flow not adjusted for body weight)                   | 3/157 (2)                                      |
| 3000 mL/h (effluent flow not adjusted for body weight)                   | 29/75 (39)                                     |
| Dialysis dose adjusted for body weight upon CRRT initiation              | 27/75 (36)                                     |
| Dialysis dose adjusted for body weight on admission                      | 19/75 (25)                                     |
| Dialysis dose adjusted for ideal total weight                            |                                                 |
Table 1 (continued)

| Questions                                                                 | Responses are n/N (%) unless otherwise indicated |
|---------------------------------------------------------------------------|--------------------------------------------------|
| Which type(s) of membrane do you use for CRRT?                           |                                                  |
| Polysulfone (Fresenius® kits: CVHDF 600, CVHDF 1000, CVVH 600, CVVH 1000, | 54/138 (39)                                      |
| HV-CVVH 1000, Ci-Ca post CVVHDF 1000, Ci-Ca CVVHD 1000, Ci-Ca EMic2,     |                                                  |
| Theradial® kits: Aquamax HF12, HF 19)                                     |                                                  |
| Polymethylenesulfone (Baxter® kits: Prismaflex HF1000, HF1400)           | 9/138 (7)                                        |
| Acrylonitrile (Baxter® kits: Prismaflex M100, M150)                      | 29/138 (21)                                      |
| Acrylonitrile coated with polyethylenimine (Baxter® kits: Prismaflex ST100, ST150) | 55/138 (40)                                      |

| Beta-lactam dosing regimens during CRRT                                     |
|---------------------------------------------------------------------------|
| Which beta-lactam dosing regimen do you prescribe for patients on CRRT?   |
| Unadjusted dosing regimen                                                | 88/157 (56)                                      |
| Full dose for 24 h and then a reduced-dosing regimen                     |                                                  |
| Full dose for 48 h and then a reduced-dosing regimen                     | 14/157 (9)                                      |
| A single loading dose before a reduced-dosing regimen                    | 20/157 (13)                                     |
| Reduced-dosing regimens all the time                                     | 3/157 (2)                                       |
| Reduced or full doses, depending on the drug compound                    | 6/157 (4)                                       |

| Do you adjust the antibiotic dose based on the dialysis dose or effluent flow?|
|-----------------------------------------------------------------------------|
| Yes                                                                         | 23/154 (15)                                     |
| No                                                                          | 131/154 (85)                                    |

| Do you use prolonged/continuous infusions for beta-lactams in patients on CRRT?|
|-----------------------------------------------------------------------------|
| Yes                                                                         | 138/157 (88)                                    |
| No                                                                          | 19/157 (12)                                     |

| If yes, for which beta-lactam?                                             |
|---------------------------------------------------------------------------|
| Piperacillin/Tazobactam                                                   | 108/119 (91)                                    |
| Cefotaxime                                                                | 63/119 (53)                                     |
| Ceftazidime                                                               | 85/119 (71)                                     |
| Cefepime                                                                  | 59/119 (50)                                     |
| Meropenem                                                                 | 47/119 (40)                                     |

| If yes, which tools do you use?                                           |
|---------------------------------------------------------------------------|
| Guide Prescription et Rein (French renal prescription handbook)           | 103/139 (74)                                    |
| Therapeutic drug monitoring                                              | 86/139 (62)                                     |
| Data from clinical studies in the literature                              | 48/139 (35)                                     |
| Dosing regimens of patients with renal failure applied to the estimated creatinine clearance rate of the patient on RRT | 6/139 (4)                                       |
| Pharmacokinetic software                                                 | 4/139 (3)                                       |
| Pharmacokinetic calculations by hand                                     | 3/139 (2)                                       |
| Other tools                                                               | 6/139 (4)                                       |

| If beta-lactam therapeutic drug monitoring is used, which pharmacokinetic/pharmacodynamic target do you use? |
|-------------------------------------------------------------------------------------------------------------|
| 40/50/70% T > MIC                                                                                     | 0/74 (0)                                           |
| 100% T > MIC                                                                                         | 12/74 (16)                                        |
| 40/50/70% T > 4 MIC                                                                                  | 4/74 (5)                                           |
| 100% T > 4 MIC                                                                                       | 39/74 (53)                                        |
| 40/50/70% T > 5 MIC                                                                                  | 0/74 (0)                                           |
| 100% T > 5 MIC                                                                                       | 7/74 (10)                                         |
| 40/50/70% T > 8 MIC                                                                                  | 0/74 (0)                                           |
| 100% T > 8 MIC                                                                                       | 12/74 (16)                                        |

| Do you sometimes call other specialists for advice on antibiotic dosing regimen adjustment for patients on CRRT? |
|----------------------------------------------------------------------------------------------------------------|
| No                                                                                                            | 92/157 (59)                                        |
| Infectious disease specialist                                                                              | 45/157 (29)                                       |
| Microbiologist                                                                                               | 16/157 (10)                                       |
| Pharmacist/pharmacologist                                                                                  | 13/157 (8)                                        |
on the antimicrobial agent in question. Only three physicians reported using reduced doses all the time. A dose adjustment could be either empirical or adapted according to the TDM results. In 85% of cases, the respondents did not adapt the beta-lactam dosing as a function of the CRRT dose or the effluent flow (85%). The physicians used mainly the French renal prescription handbook (Guide Prescription et Rein) (74%), TDM (62%), and data from the literature (35%) to adjust the beta-lactam dosing regimens. Only 4 physicians reported using pharmacokinetic software tools. When TDM was used, 100% T > MIC was the most common pharmacokinetic/pharmacodynamic (PK/PD) target. 41% of the respondents sometimes consulted another specialist when deciding whether or not to adjust the beta-lactam dose during CRRT: this was variously an infectious disease specialist (29%), a microbiologist (10%), a pharmacist/pharmacologist (8%), a nephrologist or toxicologist (5%). The replies to the clinical vignettes highlighted a broad range of dose adaptation practices - particularly for meropenem (Fig. 1). Most participants used prolonged and continuous infusions (88%), especially for piperacillin-tazobactam (91%), ceftazidime (71%), cefotaxime (53%), cefepime (50%) and meropenem (40%). Only 21% of physicians reported having access to a procedure for determining beta-lactam dosing regimens during CRRT. Only 34% of the physicians had the feeling that neurotoxicity was more frequent during CRRT. The use of TDM was significantly associated with prolonged and continuous

| Questions | Responses are n/N (%) unless otherwise indicated |
|-----------|-------------------------------------------------|
| Nephrologist | 8/157 (5) |
| Toxicologist | 8/157 (5) |
| For a 70 kg patient admitted with community-acquired infectious pneumonia and treated with your preferred CRRT technique at 25 ml/kg/hour, which maintenance dose do you prescribe for cefotaxime? | |
| 2 g TID | 84/156 (54) |
| 2 g BID | 17/156 (11) |
| 1 g TID | 44/156 (28) |
| 1 g BID | 9/156 (6) |
| 1 g QID | 2/156 (1) |
| For a 70 kg patient admitted with hospital-acquired infectious pneumonia and treated with your preferred CRRT technique at 25 ml/kg/hour, which maintenance dose do you prescribe for piperacillin/tazobactam? | |
| 4/0.5 g QID | 61/154 (40) |
| 4/0.5 g TID | 69/154 (45) |
| 4/0.5 g BID | 15/154 (10) |
| 3/0.375 g QID | 6/154 (4) |
| Other | 2/154 (1) |
| For a 70 kg patient admitted with hospital-acquired infectious pneumonia and treated with your preferred CRRT technique at 25 ml/kg/hour, which maintenance dose do you prescribe for meropenem? | |
| 2 g TID | 48/156 (31) |
| 2 g BID | 9/156 (6) |
| 1 g TID | 69/156 (44) |
| 1 g BID | 28/156 (18) |
| Other | 2/156 (1) |
| Does your institution have procedures for adjusting antibiotic doses in patients on CRRT? | |
| Yes | 33/157 (21) |
| No | 124/157 (79) |
| Do you feel that you observe more beta-lactam-induced neurotoxicity in patients treated with renal replacement than in other patients? | |
| Fully agree | 5/157 (3) |
| Tend to agree | 48/157 (31) |
| Tend to disagree | 80/157 (51) |
| Strongly disagree | 24/157 (15) |

Abbreviations: CRRT continuous renal replacement therapy, MIC minimum inhibitory concentration, BID twice a day, TID three times a day, QID four times a day
infusions ($p=0.016$) and a call to other specialists for advice on antibiotic dosing regimen adjustment during CRRT ($p<0.0001$) (Table 2).

**Discussion**

To the best of our knowledge, the present study is the first to have assessed beta-lactam dosing practices in the context of CRRT. Furthermore, the survey described CRRT practices in France. Physicians practicing intensive care medicine (whatever their initial qualification) were included in the survey. The majority were intensivists or anesthesiologists, which reflects the fact that anesthesiologists are qualified for critical care medicine in France.

In order to review beta-lactam dosing in CRRT, we analyzed compliance with the French guidelines and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [21, 22]. Our present findings were in line with studies of CRRT practices performed over the last decade [23–25]. CRRT was preferred to intermittent hemodialysis, although there is no clear evidence of superiority.
concerning reduced mortality [21, 22]. This technique is considered to provide greater hemodynamic stability. As recommended, citrate was the main anticoagulant used [21, 22]. Multicenter randomized controlled trials and meta-analyses have shown that increasing the CRRT dose intensity above 20–25 ml/kg/h does not increase survival but does lead to more metabolic complications [26–29]. Therefore, in order to deliver a dose of 20–25 ml/kg/h and to minimize interruptions in the CRRT, the KDIGO guidelines recommend a value of 25–30 ml/kg/h [22]. Although citrate limits filter coagulation, a third of our respondents indicated (as also found in other studies) that they prescribe a higher CRRT dose - leading to greater clearance of beta-lactams [23, 25]. The physicians reported using different reference body weights to prescribe the CRRT dose, which contributed to disparities in RRT practices. Although most studies are based on total weight at the time of randomization, the guidelines do not specify the weight to be used to determine the dialysis dose - resulting in a variety of practices. Our survey highlighted the diversity and lack of harmonization of CRRT techniques.

Physicians may not be sufficiently aware of the need to maintain beta-lactam full doses during the initial phase of treatment. Administration must be optimized in order to maintain effective antibiotic concentrations for a sufficiently long time and thus maximize the chances of therapeutic success. This is especially true in the initial phase of sepsis when cardiac output and capillary permeability increase and protein binding is altered; this leads to increased clearance and a larger volume of distribution, inducing low serum and tissue beta-lactams concentrations [1, 30]. Underexposure increases the likelihood of therapeutic failure and the emergence of resistance. Improving antibiotic exposure is, therefore, a major challenge. Secondly, organ dysfunctions (and especially kidney failure) lead to high serum antibiotic concentrations. CRRT may limit underdosing when using full doses with a potential risk of neurotoxicity in the event of overdosing [4, 12, 15]. The mechanisms by which antibiotics are eliminated by CRRT appear to be poorly understood since the majority of physicians do not reportedly adjust the dosage as a function of the dialysis dose or effluent flow.

Our survey highlighted the broad implementation of extended and continuous infusions and so showed that physicians were well aware of the time-dependent nature of the beta-lactams’ activity. Even though the guidelines recommending the use of extended and continuous infusions for all compounds (to increase the probability of target attainment), these modalities are still mainly used for a few beta-lactams only and adherence to guidelines is suboptimal [5, 20]. This might be due to the recent changes in the French guidelines between 2014 and 2018. The French-speaking Intensive Care Society initially recommended continuous infusions for ceftazidime and extended infusions (over 3-4 h) for a few other beta-lactams [31]. In October 2018, the French Society of Anesthesia and Intensive Care Medicine and the French Society of Pharmacology and Therapeutics suggested the use of prolonged or continuous infusion of beta-lactams (intending to increase the probability of PK/PD target attainment and clinical cure rates) but did not differentiate between the various molecules [5]. These guidelines apply to infections with high-MIC bacteria or with non-fermenting Gram-negative bacilli, in patients in shock or with high severity scores, and lower respiratory tract infections (as described in our clinical vignettes). However, these guidelines were published just a few months before our survey, which may have limited their dissemination. Continuous and extended infusions are mostly used for piperacillin-tazobactam and ceftazidime; these are the compounds for which we have the most literature data, as reported in the ANTIBIOP-ERF study performed in 2015 [32]. Continuous infusion is mentioned in the French summary of product characteristics for ceftazidime only [33]. In the last decade, several other surveys have focused on these practices. A survey of 34 Belgian hospitals in 2011 showed that four beta-lactams were administered in the ICU by continuous and extended infusion to a varying extent: in 35% of the ICUs for cefepime, 38% for piperacillin-tazobactam, 68% for meropenem, and 81% for ceftazidime [34]. In 2013, an international multicenter survey of 402 physicians in 53 countries reported that piperacillin/tazobactam and carbapenem (meropenem and imipenem) were mainly administered as intermittent infusions (71% and 68%, respectively) [35]. In 2019, a German study reported that meropenem (70%), piperacillin/tazobactam (67%) and imipenem (50%) were the beta-lactams most regularly administered as prolonged and continuous infusions [36]. A survey performed in Australia and New Zealand in 2016 focused on meropenem and piperacillin-tazobactam, which were most frequently administered in intermittent infusions [37]. The administration method may therefore differ from one geographic region to another. The survey of Australia and New Zealand highlighted the fact that the infusion modality could be determined on a case-by-case basis, depending on the presence of bacteria with high MICs, pathological changes (sepsis or sepsis shock), and the severity of the patient’s illness [37].

The prescription tools used by the majority of physicians are not designed to recommend personalized dosages, and the use of pharmacokinetic software for finer dosage adjustment is rare. However, beta-lactam TDM is increasingly being used in CRRT, in line with the
The diversity of PK/PD targets emphasizes the uncertainties in the literature data, even though most physicians are well aware that a beta-lactam concentration over several times the MIC is required throughout the dosing interval (as already reported by Wong et al. in 2014 [38]). However, few of our respondents answered this question, showing that the concept of dosage adjustment based on PK/PD indices is poorly known (as already described in the ONTAI study [36]). In 2018, the French Society of Pharmacology and Therapeutics and the French Society of Anesthesia and Intensive Care Medicine suggested that targeting a free plasma beta-lactam concentration over four times the MIC of the causative bacteria (or the EUCAST epidemiological cut-off, when the MIC of the isolated strain is not available) for 100% of the dosing interval would maximize the bacteriological and clinical responses in critical care patients, whereas the European guidelines recommend a PK/PD index of between two and five times the MIC [5].

The duration of the beta-lactam infusion was not defined in the questionnaire’s clinical vignettes; this limited the interpretation of our respondent’s practices but highlighted the diversity of dosing regimens used. Although meropenem is the best-studied beta-lactam in CRRT, its dosing regimens differed most significantly among our respondents (Table 1, Supplementary material). This variability was also evidenced in a Belgian study of ICUs and non-ICU wards [34].

Moreover, our survey results underlined the need for procedures and the importance of a multidisciplinary approach for providing stable infusions, since most physicians are not aware of the stability data [32, 34]. The fact that respondents using TDM were more likely to call other specialists and more likely to use prolonged/continuous infusions shows that TDM is part of a comprehensive, complex approach to PK/PD optimization, which also requires determination of the MIC and knowledge of the PK/PD target. The TDM included in Bayesian software represents the best option for personalizing antimicrobial dosing by taking account of various parameters (the MIC, site of infection, weight, renal function, severity, etc.). However, not all the clinical scenarios are available, and the high level of sophistication of these pharmacokinetic tools limits their implementation. Further studies are required to validate these tools and their potential clinical impact. Moreover, the variety of selected PK/PD targets raises the question of whether TDM is useful, given the resulting differences in dose adjustments. The different perceptions of neurotoxicity in patients on CRRT are probably related to the diversity of doses used, as illustrated in the replies to the clinical vignettes.

Our survey had some limitations. Firstly, the questionnaire did not fully reflect the complexity of having to decide on the dosing regimen at the bedside. The clinical vignettes and questions were simple and standardized. Secondly, the low response rate (11%) was explained by recruitment bias, since the survey was conducted during the summer vacation. Thirdly, we did not have an exhaustive list of intensivists in France. However, all types of hospitals (university or not, public or private sector, etc.) were represented. Despite these limitations, we undertook the largest yet study of this type in French ICUs. The diversity of replies to our questionnaire highlights
the uncertainties regarding dosage adjustments required in CRRT and the lack of harmonization of PK/PD targets and emphasized the need for further research on a topic that is crucial in critically ill patients.

Conclusions
The diversity of beta-lactam dosing regimens and the tools used to adjust it may be responsible for significant morbidity and mortality. Optimal antimicrobial dosing during CRRT remains challenging. Personalized TDM and the use of Bayesian softwares appear to be fundamental for optimizing beta-lactam dosing regimens and improving patients’ outcomes. However, low availability and a lack of clinical validation limit the implementation of these tools.

Abbreviations
CRRT: Continuous renal replacement therapy; EUCAST: European Committee on Antimicrobial Susceptibility Testing; ICU: Intensive care unit; IQR: Interquartile range; KDIGO: Kidney Disease: Improving Global Outcomes; MIC: Minimal inhibitory concentration; PK/PD: Pharmacokinetic/pharmacodynamic; RRT: Renal replacement therapy; TDM: Therapeutic drug monitoring.

Supplementary Information
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Additional file 1.

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Authors' contributions
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The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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