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# Impact du sepsis et de l'épuration extra-rénale sur la pharmacocinétique des antibiotiques.

Claire Penetrat-Roger

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**THESE POUR OBTENIR LE GRADE DE DOCTEUR  
DE L'UNIVERSITE DE MONTPELLIER**

**En Anesthésie-Réanimation**

**École doctorale CBS2**

**Unité de recherche EA 2992**

**IMPACT DU SEPSIS ET DE L'EPURATION EXTRA-  
RENALE SUR LA PHARMACOCINETIQUE DES  
ANTIBIOTIQUES**

*Impact of septic shock and renal replacement therapy on antimicrobial  
pharmacokinetics and pharmacodynamics.*

**Présentée par Claire ROGER PENETRAT  
Le 18 Décembre 2017**

**Sous la direction de Jean-Yves LEFRANT  
et Laurent MULLER**

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**UNIVERSITÉ  
DE MONTPELLIER**

*Il y aura des obstacles,  
Il y aura des doutes,  
Il y aura des erreurs,  
Mais si tu travailles fort,  
Il n'y aura aucune limite.*

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## ABBREVIATIONS

PK/PD : Pharmacocinétique/ Pharmacodynamie

BMR : bactéries multi-résistantes

EERc : Epuration Extra-Rénale Continue

Vd : Volume de distribution

T<sub>1/2</sub> : Temps de demi-vie

Cl : Clairance

CMI : concentration minimale inhibitrice

C<sub>max</sub> : concentration plasmatique maximale

C<sub>min</sub> : concentration plasmatique minimale

CVVHF : hémofiltration veino-veineuse continue

CVVHD : hémodialyse veino-veineuse continue

CVVHDF : hémodiafiltration veino-veineuse continue

S<sub>c</sub> : sieving coefficient

Q<sub>UF</sub> : débit d'ultrafiltrat

S<sub>d</sub> : coefficient de saturation

Q<sub>d</sub> : débit de diluats

ClCr : clairance de la créatinine

BGN : bacille à Gram négatif

## *1. INTRODUCTION*

---

Le choc septique est la cause d'admission de 30% des patients en réanimation. Malgré des progrès notables ces 20 dernières années, la mortalité associée au sepsis reste élevée, de l'ordre de 20 à 30%.<sup>1-3</sup> La survenue de défaillances d'organes et notamment de défaillance rénale aggrave encore le pronostic.<sup>4</sup> Ce pronostic est principalement conditionné par le contrôle de la source infectieuse dans lequel l'antibiothérapie joue un rôle majeur. Une littérature abondante a souligné l'importance d'administrer une antibiothérapie précoce et adaptée aux patients en choc septique afin d'en diminuer la mortalité.<sup>5-8</sup> Toutefois, la notion d'antibiothérapie adaptée est souvent peu définie et fait référence au spectre d'activité de l'antibiotique administré vis-à-vis du pathogène suspecté ou prouvé. Moins fréquemment, ceci renvoie à la notion de posologie adaptée pour obtenir des concentrations efficaces au site de l'infection. Pourtant, plusieurs travaux ont montré le risque élevé de sur- ou sous-dosage plasmatique chez les patients admis en réanimation pouvant conduire à un échec thérapeutique.<sup>9,10</sup> De plus, les recommandations de la Surviving Sepsis Campaign de 2012 apportent la précision que l'antibiothérapie administrée à la phase initiale du choc septique doit comprendre une ou plusieurs molécules ayant une activité contre l'ensemble des pathogènes potentiellement en cause et diffusant à des concentrations suffisantes dans les tissus infectés.<sup>11</sup> La garantie de concentrations thérapeutiques au site de l'infection est cependant difficile à obtenir dans la pratique courante chez les patients septiques. En effet, le sepsis est à l'origine de modifications majeures de la pharmacocinétique (PK) des antibiotiques telles que l'augmentation du volume de distribution, l'hypoalbuminémie et/ou la modification des clairances corporelles.<sup>12</sup> Le recours à l'épuration extra-rénale ajoute un degré supplémentaire de complexité pour déterminer la posologie optimale d'antibiotique permettant d'obtenir des taux plasmatiques efficaces pour ces patients.<sup>13,14</sup> Il est donc

nécessaire d'obtenir des données pharmacocinétiques/pharmacodynamiques (PK/PD) permettant d'administrer la « bonne » dose au « bon moment » et au « bon » patient.

La mise sur le marché d'un nouvel antibiotique est un processus réglementaire complexe dans lequel l'analyse PK/PD joue un rôle primordial. Toutefois, la population de patients de réanimation et en particulier des patients en choc septique n'est jamais considérée dans les premières phases de développement (phase 1) et très rarement dans les phases plus avancées (phases 2 et 3). Ceci pose un problème essentiel car les posologies usuelles recommandées dans la population de patients stables s'avèrent souvent inadaptées, parfois toxiques pour les patients présentant des défaillances d'organes.<sup>10,15-17</sup> Ces quinze dernières années, une littérature croissante portant sur l'intérêt de l'analyse PK/PD des antibiotiques utilisés en réanimation a tenté de répondre à cette problématique.<sup>18-21</sup> Il convient de ne pas perdre de vue l'objectif principal de cette approche PK/PD : la capacité à prédire le schéma posologique associé à l'efficacité d'un traitement anti-infectieux tout en limitant la toxicité et la résistance bactérienne. En effet, le bon usage des antibiotiques est une priorité de santé publique.<sup>22,23</sup> L'émergence de la résistance bactérienne constitue un problème majeur qui selon le rapport O'Neil pourrait représenter la cause première de mortalité à l'horizon 2050.<sup>24</sup> Les patients de réanimation représentent une population particulièrement à risque à la fois d'échec thérapeutique dont les conséquences peuvent être fatales mais également à risque de voir se développer des bactéries multi-résistantes (BMR). Le recours à l'épuration extra-rénale continue (EERc) va être à l'origine d'une nouvelle voie d'élimination des antibiotiques qui sera plus ou moins prédominante selon l'antibiotique considéré et la technique d'EER utilisée.<sup>25</sup> Tous ces facteurs pris en compte, il devient très difficile de connaître la dose à administrer à un patient en choc septique sous EERc.

Le but de ce travail de thèse était d'évaluer l'impact de l'épuration extra-rénale et du sepsis sur différentes classes d'antibiotiques fréquemment administrés en réanimation et d'en définir

les posologies les plus adaptées. Pour cela nous avons choisi dans un premier temps d'analyser l'impact du sepsis sur la PK d'une classe d'antibiotique présentant une fenêtre thérapeutique étroite : les aminosides. Dans un second temps, nous avons élaboré une analyse PK de population en développant des modèles PK/PD permettant de supporter des simulations de Monte Carlo dans le but d'identifier le schéma posologique optimal dans cette population « à haut risque » représentée par les patients en choc septique sous EERc, soit en hémofiltration veino-veineuse continue (CVVHF) soit en hémofiltration veino-veineuse continue (CVVHDF).

## *2. INTERET DE L'APPROCHE PK/PD*

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La pharmacocinétique d'un médicament relie les doses de médicament administrées aux concentrations plasmatiques observées et décrit leur évolution au cours du temps dans l'organisme. La pharmacodynamie est définie comme la relation entre les concentrations plasmatiques observées et les effets pharmacologiques obtenus. L'analyse PK/PD représente donc la relation entre les doses de médicaments administrées et les effets pharmacologiques observés.

### *a) Bases de pharmacocinétique*

L'utilisation optimale d'un médicament quel qu'il soit nécessite quelques connaissances PK afin de choisir le mode d'administration et les ajustements posologiques les plus adaptés à la population étudiée et au type de molécule utilisée.

Le « devenir » du médicament dans l'organisme peut être décomposé en quatre phases :

- une phase d'**absorption**, qui correspond au passage du médicament de son site d'administration vers la circulation systémique

- une phase de **distribution**, correspondant à la diffusion du médicament dans les différents tissus de l'organisme
- une phase de **métabolisme**, décrivant la transformation du médicament par l'organisme
- une phase d'**élimination**, s'intéressant aux différents processus impliqués dans l'élimination du médicament par l'organisme.

L'approche PK va déterminer plusieurs paramètres reflétant ces différentes phases dont les principaux sont :

- la **biodisponibilité** (F) qui représente la fraction de médicament administrée atteignant la circulation systémique ainsi que la vitesse permettant de l'atteindre. Elle reflète la phase d'absorption.
- le **volume de distribution** (Vd) ou volume apparent de distribution qui correspond à un volume fictif dans lequel se distribuerait le médicament s'il était à la même concentration que celle obtenue dans le sang. Ce volume reflète la phase de distribution.
- le **temps de demi-vie** ( $t_{1/2}$ ) qui correspond au temps nécessaire pour que la concentration sanguine de cette substance diminue de moitié dans sa phase d'élimination. Il reflète à la fois les phases d'élimination et de métabolisme.
- la **clairance** (Cl) qui représente le volume sanguin totalement épuré de la molécule par unité de temps. Cette clairance peut être calculée pour l'ensemble de l'organisme ou par organe. Elle reflète les phases d'élimination et de métabolisme.

Trois autres paramètres pharmacocinétiques d'intérêt sont :

- la concentration plasmatique maximale (**C<sub>max</sub>** ou « pic ») obtenue après la phase de distribution,
- la concentration plasmatique minimale (**C<sub>min</sub>** ou « résiduelle ») obtenue à la fin d'un intervalle de dose,

- l'aire sous la courbe de concentration d'antibiotique en fonction du temps (**AUC**) qui représente l'exposition totale à l'antibiotique sur un intervalle de temps défini.

Toutes ces phases peuvent être modifiées par la présence d'un processus infectieux avec un degré de magnitude différent. Ceci explique le caractère relativement imprévisible des concentrations plasmatiques observées dans cette population comme nous allons le voir ultérieurement.<sup>9</sup>

La pharmacodynamie (PD) s'intéresse à la réponse biologique de l'organisme à un médicament. Ce médicament va agir par l'intermédiaire d'un site d'action et être responsable d'un ou plusieurs effets thérapeutiques (effet recherché) ou toxiques (effets indésirables). Ces effets ne sont toutefois pas toujours facilement mesurables en pratique clinique. Dans le cas des antibiotiques, la cible d'action n'est pas une partie de l'organisme humain mais une cible bactérienne présente dans cet organisme. Il en résulte une interaction complexe impliquant trois entités : le micro-organisme (bactérie), l'hôte (le corps humain) et le médicament (antibiotique). La PD des antibiotiques relie les paramètres PK de ces antibiotiques à leur capacité à diminuer l'inoculum bactérien ou à inhiber la croissance.

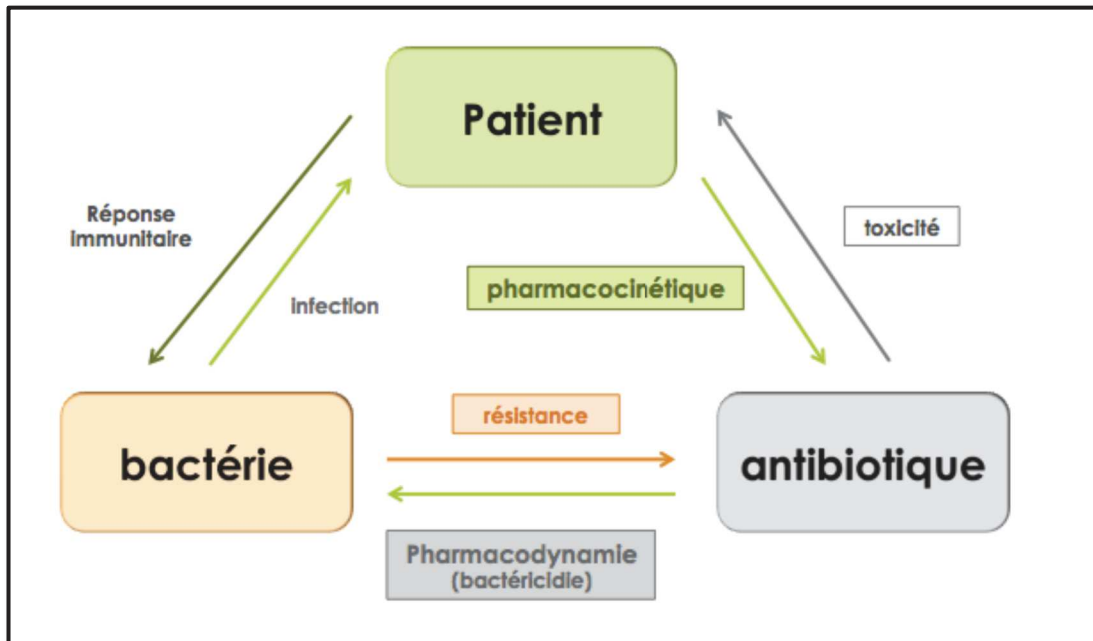


Figure 1 : Interaction hôte – bactérie – antibiotique

Il devient évident que trois éléments vont jouer un rôle majeur dans l'efficacité thérapeutique de l'antibiotique :

- 1° les **concentrations tissulaires** obtenus au site de l'infection
- 2° la **sensibilité du micro-organisme** responsable de l'infection à l'antibiotique administré
- 3° la **réponse immunitaire** de l'organisme vis-à-vis de la bactérie

Bien que très intéressant, le rôle de la réponse immunitaire dans l'efficacité de l'antibiothérapie ne sera pas abordé dans ce travail.

L'analyse idéale consisterait à considérer directement la population bactérienne hébergée par le patient et l'effet du traitement sur cette population. Cette analyse n'étant pas possible en pratique clinique, l'analyse de l'effet des antibiotiques sur la croissance d'une population de bactéries viables, celle-ci constituant elle-même un modèle de la population de bactéries responsables de l'infection chez le patient est une alternative acceptable. Un antibiotique actif sera capable d'empêcher la croissance, voire de réduire le nombre de



bactéries présentes dans un milieu de culture, dans des conditions d'utilisation données. Cet effet varie selon les conditions expérimentales, en particulier selon la concentration en antibiotique. Afin de quantifier cette relation entre la concentration d'antibiotique et l'effet observé, est définie *in vitro* la concentration minimale inhibitrice (CMI) qui correspond à la plus faible concentration d'antibiotique capable d'inhiber toute croissance bactérienne visible, après 18 à 24h d'incubation à partir d'un inoculum de quelques milliers de bactéries ( $5.10^5$  à  $2.10^8$  selon la méthode utilisée).<sup>26</sup> Selon la valeur de la CMI, le germe est classé comme sensible (CMI basse), intermédiaire, ou résistant à l'antibiotique considéré (CMI haute). Toutefois, la connaissance de la valeur exacte de CMI pourrait être plus informative pour l'optimisation PK/PD mais est difficile à obtenir en pratique courante du fait d'un coût humain important. Toutefois, l'EUCAST met à disposition une base de données (disponible sur [www.eucast.org](http://www.eucast.org)) des distributions des CMI rencontrées en Europe pour la majorité des pathogènes. Ces bases de données peuvent être utilisées dans l'analyse PK/PD afin de tenir compte de la fréquence et la distribution des CMI rencontrées dans la pratique clinique pour les pathogènes les plus fréquemment incriminés.

### ***b) Mécanismes de bactéricidie***

La notion de mécanismes de bactéricidie est importante à connaître car elle va en grande partie conditionner le mode d'administration des antibiotiques.

On distingue :

- la bactéricidie temps-dépendante, lente dont l'intensité va dépendre du temps de contact avec la cible bactérienne et de la concentration seuil.
- la bactéricidie concentration-dépendante, rapide et intense, dont la vitesse va dépendre de la concentration d'antibiotique au site de l'infection.

L'analyse *in vitro* de la vitesse de bactéricidie en fonction de la concentration croissante d'antibiotique (time kill curves en anglais) permet de définir le mécanisme de bactéricidie pour chaque classe d'antibiotique.<sup>27,28</sup>

Certaines classes d'antibiotiques vont présenter une activité concentration et temps dépendante. La classification des antibiotiques fréquemment administrés en réanimation selon leur principale caractéristique de bactéricidie est résumée dans le **tableau 1**.

ATB temps dépendants	ATB temps et concentration dépendants	ATB concentration dépendants
Béta-lactamines Erythromycine, Clarithromycine Lincosamide	Fluoroquinolones Azithromycine Glycopeptides Tigecycline Linezolid Echinocandines Triazolés Colistine	Aminosides Métronidazole Daptomycine

Tableau 1. Classification des antibiotiques selon leur mécanisme de bactéricidie.

### *c) Indices PK/PD*

Majoritairement définis à partir de modèles *in vitro* et/ou *in vivo* standardisés, trois indices PK/PD ont été rapportés comme associés à l'efficacité thérapeutique des antibiotiques<sup>29-31</sup> :

- le ratio de  $C_{max}$  sur CMI :  $C_{max}/CMI$

- le temps pendant lequel les concentrations plasmatiques restent au-dessus de la CMI lors d'un intervalle de dose :  $T > CMI$ , le plus souvent exprimé en pourcentage de l'intervalle de dose ( $\%T > CMI$ )

- le ratio de l' $AUC_{0-24}$  sur CMI :  $AUC_{0-24}/CMI$

Pour les antibiotiques présentant une activité bactéricide concentration-dépendante (par exemple les aminosides), l'indice PK/PD associé à l'efficacité clinique est représenté par la  $C_{max}/CMI$ .<sup>32,33</sup> Toutefois, certains auteurs ont suggéré que l'indice  $AUC_{0-24}/CMI$

représentant l'exposition totale journalière pourrait être un meilleur indice corrélé à l'efficacité et à la toxicité.<sup>34</sup>

Pour les antibiotiques présentant une activité bactéricide temps-dépendante (par exemple les bêta-lactamines), l'indice PK/PD à considérer est le  $T > CMI$ . Selon la molécule utilisée, cet indice peut varier de 40% à 70% chez les patients stables et jusqu'à 100% pour les patients en choc septique.<sup>9,35</sup>

Pour les antibiotiques présentant une activité bactéricide concentration-dépendante avec un degré de temps dépendance, c'est l'indice AUC/CMI qui reflètera le mieux l'efficacité thérapeutique.

#### *d) Caractéristiques physico-chimiques*

Une autre manière de classer les antibiotiques consiste à se baser sur les propriétés physico-chimiques des antibiotiques :

- les antibiotiques lipophiles tels que le linézolide, les fluoroquinolones, les macrolides vont présenter les caractéristiques communes suivantes : un large volume de distribution, une pénétration intracellulaire élevée et sont principalement métabolisés par voie hépatique.

- les antibiotiques hydrophiles tels que les bêta-lactamines, les aminosides, les glycopeptides présentent un volume de distribution faible, une pénétration intracellulaire faible et sont principalement éliminés par voie rénale.

Ces propriétés physico-chimiques distinctes expliquent l'utilisation préférentielle de certaines classes d'antibiotiques pour traiter, par exemple, des germes intracellulaires ou lorsque le but de l'antibiothérapie est d'obtenir une diffusion élevée dans des tissus « réputés » difficiles à atteindre.

Les voies principales d'élimination n'étant pas les mêmes, on comprend aisément que ces deux classes d'antibiotiques ne vont pas être affectées de la même façon par les dysfonctions d'organe telles que la dysfonction rénale et la dysfonction hépatique.

### ***3. ALTERATIONS DE LA PHARMACOCINETIQUE DES ANTIBIOTIQUES INDUITES PAR LE SEPSIS***

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Le sepsis est une pathologie complexe responsable dans sa forme la plus grave de défaillances d'organe et d'une atteinte microcirculatoire prédominante. La barrière endothéliale des micro-vaisseaux joue un rôle primordial dans plusieurs fonctions de l'organisme dont les principales sont le maintien de l'homéostasie et la perméabilité capillaire.<sup>36</sup> Les atteintes endothéliales liées au sepsis vont entraîner une perte de l'intégrité de la membrane endothéliale secondaire à une destruction du glycocalyx, enchevêtrement de glycoprotéines régulant le passage transmembranaire.<sup>37</sup> Ces altérations de l'endothélium vasculaire induites par le sepsis vont être à l'origine d'une hyperperméabilité capillaire et d'oedème interstitiel aggravant l'hypoperfusion tissulaire et la défaillance d'organes.<sup>38</sup>

Ces altérations liées au sepsis vont exposer les patients au risque de sous ou surdosage lorsque des posologies conventionnelles d'antibiotiques sont utilisés dans cette population. **Article 1.**

#### ***a) Augmentation du volume de distribution (Vd)***

L'hyperperméabilité capillaire favorisant la fuite de liquide du secteur intravasculaire vers l'interstitium est responsable d'un troisième secteur qui augmente le volume dans lequel l'antibiotique va se distribuer. Cette augmentation du Vd impacte principalement les

molécules hydrophiles et a pour conséquence la nécessité d'utiliser des doses d'antibiotiques plus élevées comme nous allons le voir dans les **Articles 1 et 2**.

**Article 1 : Les doses conventionnelles d'aminosides conduisent à des concentrations plasmatiques sub-thérapeutiques chez les patients en choc septique.**

Les aminosides sont des antibiotiques hydrophiles qui ont, par conséquent, un volume de distribution faible et une élimination rénale élevée de l'ordre de 90-98%.<sup>39</sup> Leur bactéricidie, rapide et intense, est concentration-dépendante. Les travaux de Moore et al. ont démontré que le ratio  $C_{max}/CMI$  était corrélé au succès thérapeutique.<sup>32</sup> Ces résultats ont été confirmés plus récemment par Duszynska et al. qui renaient un seuil de  $C_{max}/CMI$  à 10 corrélé à l'efficacité clinique et à l'éradication bactérienne.<sup>33</sup> Les recommandations françaises de l'ANSM (anciennement AFSSAPS) préconisent une cible thérapeutique de 60 mg/L pour l'amikacine et de 30 à 40 mg/L pour la gentamicine.<sup>40</sup> De plus, ces recommandations préconisent le monitoring des concentrations résiduelles pour évaluer le risque de néphrotoxicité avec des cibles de 2,5 mg/L pour l'amikacine et de 0,5 mg/L pour la gentamicine. Nous avons donc, dans un travail prospectif, cherché à évaluer la proportion de patients parmi les patients en choc septique recevant des doses conventionnelles d'aminosides (15 à 30 mg/kg d'amikacine, 5 à 8 mg/kg de gentamicine) qui présentait des concentrations plasmatiques maximales et/ou résiduelles en dehors des cibles thérapeutiques recommandées. Pour cela, 90 patients en choc septique pour lesquels des concentrations plasmatiques d'aminosides étaient disponibles ont été inclus. L'amikacine (n=66) et la gentamicine (n=24) étaient administrées à la dose moyenne de  $22,6 \pm 6,9$  mg/kg et  $6,6 \pm 2,3$  mg/kg respectivement, pour un sepsis dont l'origine était pulmonaire, abdominale ou urinaire dans plus de 2/3 des cas.

Les résultats de cette étude ont mis en évidence :

- une variabilité inter-individuelle majeure
- une proportion conséquente (77% pour l'amikacine, 94% pour la gentamicine) de patients en choc septique présentant des  $C_{max}$  sub-thérapeutiques
- un allongement de l'intervalle de dose en rapport avec des concentrations résiduelles trop élevées pour 21 /66 patients recevant de l'amikacine et 2 /24 patients recevant de la gentamicine.

**Conclusion : Ce travail a donc confirmé l'impact du sepsis sur la PK des aminosides conduisant à un sous-dosage plasmatique pour plus de 2/3 des patients et une diminution de la clairance conduisant à des concentrations plasmatiques résiduelles trop élevées pour 1/3 des patients de l'étude. Nous avons dans un second travail prospectif évalué l'impact de l'administration de posologies élevées d'aminosides (30 mg/kg pour l'amikacine et 8 mg/kg pour la gentamicine) à la phase précoce du sepsis sur la probabilité d'atteindre les cibles thérapeutiques recommandées. Article 2.**

# Article 1. Les doses conventionnelles d'aminosides sont à l'origine de concentrations plasmatiques variables et sub-thérapeutiques. *IJAA* rang B, impact factor 2015 : 4.3.<sup>41</sup>

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## Standard dosing of amikacin and gentamicin in critically ill patients results in variable and subtherapeutic concentrations



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### ABSTRACT

Low peak plasma concentrations ( $C_{max}$ ) of amikacin and gentamicin are reported in intensive care unit (ICU) patients after administration of the first dose. The present study aimed to describe the proportion of ICU patients in whom an adequate  $C_{max}$  was achieved throughout the course of therapy. Septic ICU patients with an indication for intravenous amikacin or gentamicin were eligible for inclusion in this single-centre observational study. The first and subsequent doses and the corresponding  $C_{max}$  values were recorded. The target  $C_{max}$  was  $\geq 60$  mg/L for amikacin and  $\geq 30$  mg/L for gentamicin. Amikacin and gentamicin plasma concentrations were available in 66 and 24 patients, respectively ( $59 \pm 17$  years;  $79 \pm 19$  kg; height  $169 \pm 12$  cm; SAPS II score  $46 \pm 19$ ). Pulmonary, abdominal and urinary tract infections were diagnosed in 64 patients. Culture-positive infection was confirmed in 65 patients (72%). A target first  $C_{max}$  was achieved in 17/90 patients (19%). For amikacin, the target  $C_{max}$  was achieved in 16/66 patients (24%) after the initial dose. In the 50 remaining patients, a change in dosing was performed in 14 patients, leading adequate peak plasma level in 2 patients. For gentamicin, the targeted  $C_{max}$  was achieved in only 1/24 patient (4%) after the initial dose and was never achieved after the third dose. In conclusion, standard dosing of amikacin or gentamicin led to adequate  $C_{max}$  in only 19% of patients. Subtherapeutic  $C_{max}$  were not significantly corrected after subsequent doses.

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### 1. Introduction

Early and appropriate treatment of infections is a priority in the management of intensive care unit (ICU) patients and could reduce mortality rates in patients with severe sepsis or septic shock [1,2]. Therefore, empirical broad-spectrum anti-infective therapy, often using multiple agents, is recommended for the initial treatment

of severe sepsis [3]. Although some specific anti-infective combinations remain controversial, a survival improvement has been reported with the use of combination therapy in patients with septic shock [4,5]. Therefore, aminoglycosides are often given as part of empirical therapy for severe sepsis and septic shock, especially when Gram-negative bacteria are suspected [6].

One of the main conditions for aminoglycoside therapy to be efficient is to achieve therapeutic drug concentrations at the site of infection [7]. As tissue concentrations of anti-infective drugs cannot be routinely measured, plasma concentrations are classically used as a surrogate to confirm the appropriateness of dosing and anti-infective exposure. From a pharmacodynamic perspective, for aminoglycosides the ratio between the peak plasma concentration ( $C_{max}$ ) and the minimum inhibitory concentration (MIC) of the

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infecting pathogen ( $C_{\max}/\text{MIC}$ ) is considered as the best index of bacterial killing and the subsequent success of anti-infective treatment [8]. Maximum antibacterial activity is achieved when  $C_{\max}$  is 8–10 times greater than the MIC [9–11]. Although the ratio of the area under the concentration–time curve from 0–24 h ( $\text{AUC}_{0-24}$ ) to the MIC ( $\text{AUC}_{0-24}/\text{MIC}$ ) for the first dose is also correlated with maximum aminoglycoside activity [12], for convenience peak concentrations are used for therapeutic concentration monitoring [13]. Despite a large possible distribution of MICs for different pathogens, recent French recommendations for the use of aminoglycosides targeted  $C_{\max}$  of 30–40 mg/L and 60–80 mg/L for gentamicin and amikacin, respectively [14]. These recommendations are closest to the recommended peak concentrations in recent publications [15–17]. As aminoglycosides are nephrotoxic, residual plasma concentrations should be monitored to minimise the likelihood of nephrotoxicity and ototoxicity [13,14].

Although the pharmacokinetics of aminoglycosides in ICU patients has previously been described, studies on optimal dosing regimens for patients with sepsis have had several limitations [18,19]. Many factors can influence the pharmacokinetics of different anti-infective drugs [20]. Indeed, alterations in the volume of distribution, plasma albumin concentration, increased cardiac output, increased blood volume, and paradoxical renal and hepatic clearance increase can be observed in the early stage of severe sepsis and are frequently observed in ICU patients [20]. Some studies have previously shown a low aminoglycoside concentration in the early phase of therapy in ICU patients [17,21]. Taccone et al. [17] and de Montmollin et al. [15] recently reported 30% and 33% of patients with a first amikacin  $C_{\max}$  of <60 mg/L after a first dose of 25 mg/kg, respectively. Gálvez et al. [16] compared three initial doses of amikacin (15, 25 and 30 mg/kg) and reported a target  $C_{\max}$  of >60 mg/L in 0%, 39% and 76% of patients, respectively. Unfortunately, neither of these previous studies provided concentration data for the subsequent doses of aminoglycosides. Therefore, to address this deficiency in the literature, an observational study was performed to describe the proportion of ICU patients achieving target peak plasma aminoglycoside concentrations after the first dose as well as after subsequent aminoglycoside doses.

## 2. Materials and methods

This was a single-centre observational cohort study. As this was a non-interventional study to assess the daily practice of aminoglycoside monitoring in the ICU of Nîmes University Hospital (Nîmes, France), approval by the Comité de Protection des Personnes was not required according to French law. Therefore, the study was approved by the Institutional Review Board of Nîmes University Hospital and was declared to the Commission nationale de l'informatique et des libertés (CNIL). For this reason, the need for written informed consent from patients was waived. However, all patients and/or their next of kin were verbally informed of the data collection and could refuse to participate.

All ICU patients with infection in whom the physician in charge prescribed intravenous (i.v.) administration of aminoglycosides were eligible for inclusion. Patients were excluded if they were <18 years of age or had a known allergy to aminoglycosides. Finally, patients who were under guardianship or prisoners could not participate. Patients with a confirmed and/or suspected myasthenia and/or ICU-acquired neuromuscular disorder were also excluded. No patient was included more than once in the data collection.

The aminoglycoside was given in combination with broad-spectrum antibiotics according to the suspected pathogens and to local clinical practice. In our ICU, a once-daily dosing regimen is used as follows:  $\geq 15$  mg/kg for amikacin and  $\geq 3$  mg/kg for gentamicin based on actual weight at admission. For obese patients,

the weight used for dosing was left to the physician's discretion. All aminoglycosides were given as a 30-min i.v. infusion in glucose 5% solution. The timing of  $C_{\max}$  sampling was 30 min after the end of initial infusion. When subsequent doses of aminoglycoside were recommended as part of the patient's treatment plan, trough plasma concentrations (taken at 16–24 h post-infusion) ( $C_{\min}$ ) and  $C_{\max}$  were collected as part of unit practice.

The targeted concentrations for amikacin and gentamicin were as follows [14]: amikacin, peak  $\geq 60$  mg/L and trough <2.5 mg/L; and gentamicin, peak  $\geq 30$  mg/L and trough <0.5 mg/L.

The following data were collected:

- demographic characteristics: age, sex, and height and weight with calculated body mass index (BMI);
- medical history, initial reason for ICU admission and Simplified Acute Physiology Score II (SAPS II) [22] at ICU admission;
- clinical parameters: urine output was classically collected every 2 h; the Sequential Organ Failure Assessment (SOFA) [23] score and the Acute Kidney Injury Network (AKIN) [24] score were calculated daily from the initiation of aminoglycoside therapy;
- presence of renal replacement therapy (RRT);
- co-prescription of nephrotoxins (e.g. glycopeptides, diuretics);
- biological parameters: serum creatinine concentration, hepatic function (serum total bilirubin and transaminase) and platelets that were daily dosed in daily practice;
- type of infection and anti-infective therapy: type of infection, anti-infective agent(s) administered and microbiological cultures collected; and
- amikacin and gentamicin assays: amikacin and gentamicin concentrations were measured using automated immunoassays (Roche Diagnostics GmbH, Mannheim, Germany) on a COBAS® C System. Three levels of quality controls were performed daily (5, 14 and 27 mg/L for amikacin and 1.7, 4.5 and 6.8 mg/L for gentamicin). As mentioned in the supplier's data sheet, the limit of quantification is 0.8 mg/L for amikacin and 0.3 mg/L for gentamicin.

### 2.1. Statistical analysis

Data are expressed as the mean  $\pm$  standard deviation (S.D.) for quantitative variables. Qualitative data are expressed as absolute values with percentage.

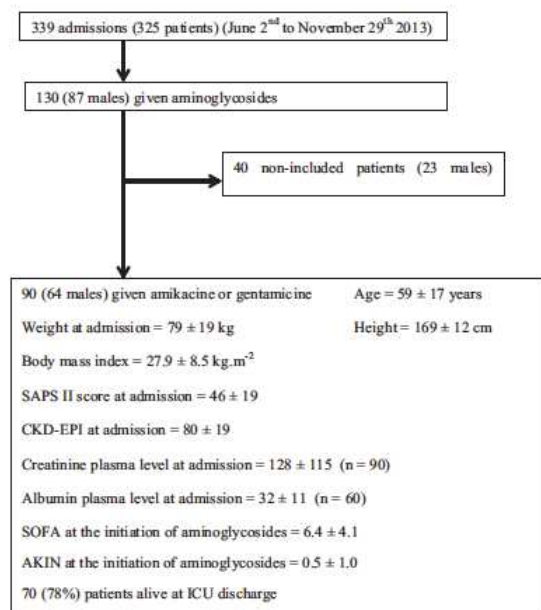
A univariate analysis and a multivariate regression model using stepwise selection were performed to determine predictive factors of not achieving target  $C_{\max}$ . When groups were compared, Mann–Whitney *U*-test, Student's *t*-test and  $\chi^2$  test were performed as appropriate. Statistical significance was set at  $P < 0.05$ .

## 3. Results

### 3.1. Patients

From 2 June 2013 to 29 November 2013, 325 patients (197 male; age  $61 \pm 17$  years; SAPS II score  $40.4 \pm 20.2$ ; length of stay in the ICU  $7.9 \pm 12.6$  days; mortality rate 30%) were admitted to the ICU. Among them, 130 patients (87 male) were administered aminoglycosides (Fig. 1). Tobramycin was given to 6 patients who did not participate and in another 34 patients a concentration from the first dose of aminoglycosides was not available; thus, 90 eligible patients were included in the study (Fig. 1). The characteristics of the patient cohort are shown in Fig. 1. At the time of initiation of antibiotics, SOFA and AKIN scores were  $6.4 \pm 4.1$  and  $0.5 \pm 1.0$ , respectively. RRT was applied in 16 patients (18%) and concurrent nephrotoxic agents were given to 39 patients (43%).





**Fig. 1.** Flow chart for study inclusion and characteristics of the patient cohort. There was no statistical difference between included and non-included patients. SAPS II, Simplified Acute Physiology Score II; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration (formula to estimate the glomerular filtration rate); SOFA, Sequential Organ Failure Assessment score; AKIN, Acute Kidney Injury Network score; ICU, intensive care unit.

### 3.2. Infections

As described in Table 1, pulmonary, abdominal and urinary tract infections were diagnosed in more than two-thirds of patients. Culture-positive infection was present in 65 patients (72%). Gram-positive bacteria, Gram-negative bacteria and both pathogens were present in 22 (24%), 26 (29%) and 6 (7%) patients, respectively. *Staphylococcus aureus* and *Escherichia coli* were the most commonly isolated pathogens. Polymicrobial infection was diagnosed in 11 patients (12%) and yeast was isolated in 11 patients (12%).

### 3.3. Aminoglycoside therapy

#### 3.3.1. Efficacy of the first dose

Amikacin and gentamicin were given in 66 (73%) and 24 (27%) patients, respectively. Fig. 2 shows the individual  $C_{max}$  according to the given dose of amikacin or gentamicin. Seventeen patients (19%) had a  $C_{max}$  above the recommended target. Using a multivariate regression model with stepwise selection, only a low first dosing of aminoglycoside was associated with a low first  $C_{max}$  ( $P < 0.01$ ).

#### 3.3.2. Amikacin therapy (66 patients)

The mean  $\pm$  S.D. first dose was  $22.6 \pm 6.9$  mg/kg (median 21.9 mg/kg) of ICU admission body weight. Seven patients were given  $< 15$  mg/kg. The mean  $\pm$  S.D.  $C_{max}$  was  $50.9 \pm 19.1$  mg/L. Sixteen patients (24%) given amikacin had an actual  $C_{max}$  above the recommended peak value (Fig. 2A).

The peak and trough concentrations during the treatment course are shown in Fig. 3A. From Day 2 to Day 5, 6/27, 3/33, 1/19 and 4/10 patients, respectively, had an actual  $C_{max} \geq 60$  mg/L. The median dose of amikacin did not change throughout therapy, although 75% of  $C_{max}$  concentrations were  $< 60$  mg/L (Fig. 3A).

**Table 1**  
Types of infection and pathogens.

	n
Site of infection	
Pulmonary	39
Abdominal	12
Urinary tract	13
Septicaemia	9
Other	3
Unknown	13
Isolated pathogens in 65 patients (72%)	
<i>Staphylococcus aureus</i>	15
Other staphylococci	6
<i>Enterococcus faecalis</i>	5
<i>Haemophilus influenzae</i>	2
<i>Escherichia coli</i>	11
<i>Klebsiella pneumoniae</i>	8
<i>Proteus mirabilis</i>	3
<i>Enterobacter aerogenes</i>	4
<i>Enterobacter cloacae</i>	3
<i>Serratia marcescens</i>	3
<i>Pseudomonas aeruginosa</i>	4
<i>Candida albicans</i>	11
None	25

Dosing of amikacin was increased in 14 of 50 patients with a first  $C_{max} < 60$  mg/L. These results led to an adequate  $C_{max}$  in two patients at Day 5. Fig. 3B shows the course of treatment with amikacin. The therapy was ended between Day 3 and Day 5. When a new injection was performed, the subsequent  $C_{max}$  was measured in 27/45, 33/44, 19/28 and 10/11 patients at Days 2, 3, 4 and 5, respectively (Fig. 3B).

Among 16 patients with  $C_{max} \geq 60$  mg/L, there were 4 deaths (25%) versus 14 deaths (28%) among 50 patients with  $C_{max} < 60$  mg/L ( $P = 0.82$ ).

#### 3.3.3. Gentamicin therapy (24 patients)

The mean  $\pm$  S.D. first dose of gentamicin was  $6.6 \pm 2.3$  mg/kg (median 5.9 mg/kg). No patient was given  $< 3$  mg/kg. The mean  $\pm$  S.D.  $C_{max}$  was  $15.7 \pm 7.3$  mg/L. Twenty-three patients (96%) given gentamicin had an actual  $C_{max}$  under the recommended peak value (Fig. 2B).

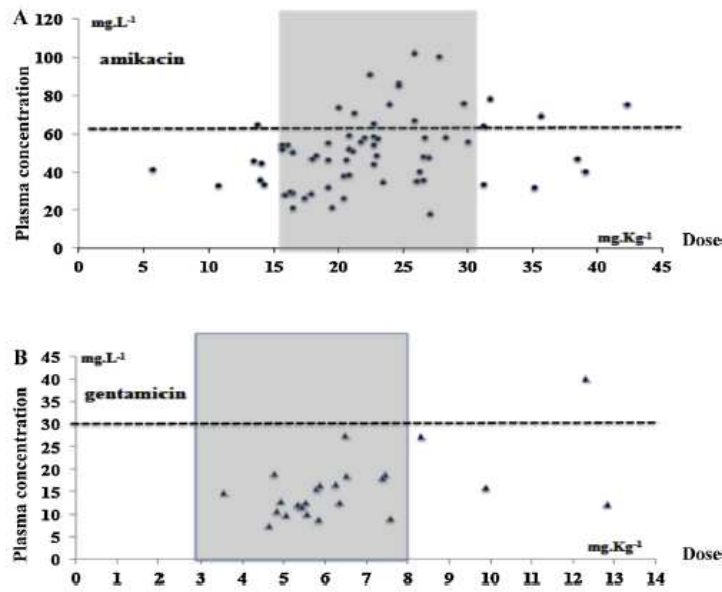
The peak and trough concentrations of gentamicin during the treatment course are shown in Fig. 4. Although the median given dose was two-fold higher than the recommended dose, a target  $C_{max}$  was reached in only one patient at Day 1 and Day 2 and was not achieved on any other days of therapy. From Day 2 to Day 5, 1/17, 0/15, 0/11 and 0/3 patients, respectively, had an actual  $C_{max} \geq 30$  mg/L (Fig. 4A). Among 23 patients with a first  $C_{max} < 30$  mg/L, there were one, two or three increases in dosing of gentamicin in 8, 4 and 1 patients, respectively.

These results never led to an adequate  $C_{max}$ . Fig. 4B shows the course of treatment with gentamicin. The therapy was ended between Day 2 and Day 5. When a new injection was performed, the subsequent  $C_{max}$  was measured in 17/20, 15/16, 11/15 and 3/7 patients at Days 2, 3, 4 and 5, respectively (Fig. 4B).

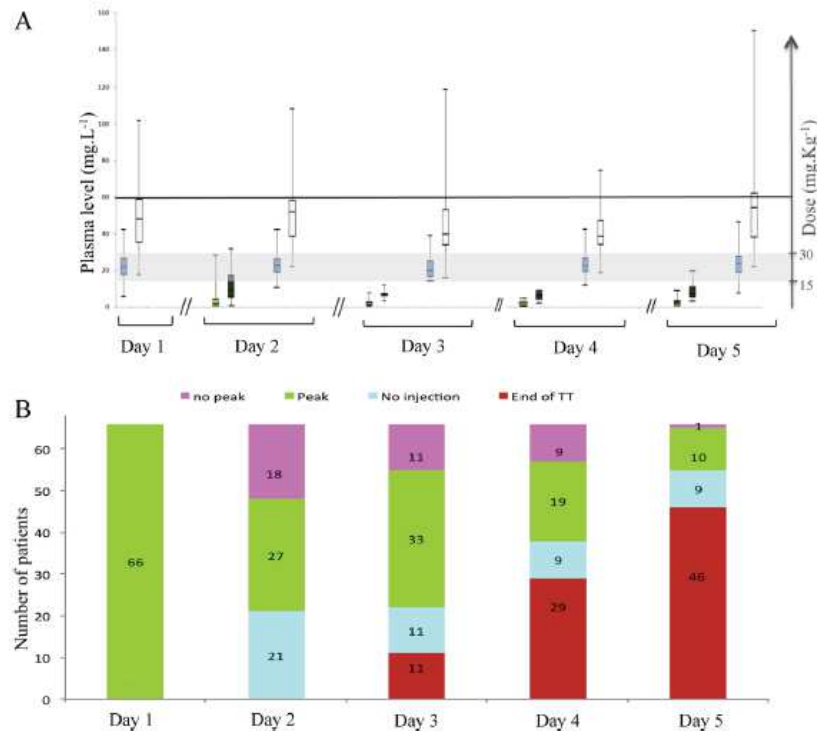
Among these 24 patients, there were two deaths with first  $C_{max}$  at 11.5 mg/L and 18 mg/L, respectively.

## 4. Discussion

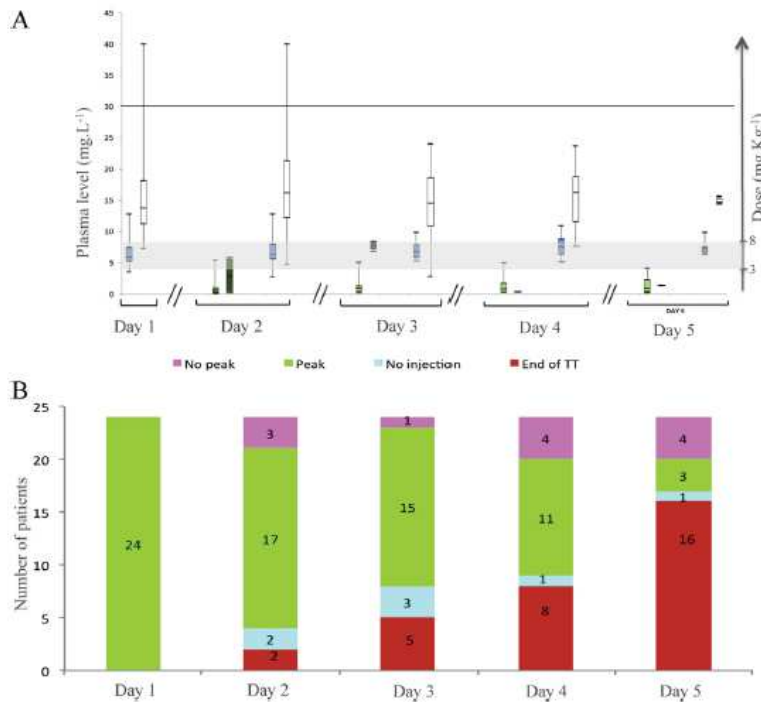
The present study assessed the daily practice of amikacin and gentamicin administration relative to a French aminoglycoside dosing guideline [14]. A first  $C_{max}$  was performed in 90 of 130 patients administered aminoglycosides. An adequate first  $C_{max}$  was reported in only 17 (19%) of 90 patients (16/66 for amikacin and 1/24 for gentamicin). For subsequent doses, when  $C_{min}$  and  $C_{max}$



**Fig. 2.** Peak plasma concentration (mg/L) according to the given dose (mg/kg) for the first dose of (A) amikacin and (B) gentamicin. The dotted line shows the recommended peak plasma concentration (mg/L). The grey zone shows the recommended dose (mg/kg).



**Fig. 3.** (A) Course of dosing, and peak and trough plasma concentrations of amikacin according to the day of therapy. Dosing is shown in the blue box plot and peak plasma concentrations in the white box plot. Trough plasma concentrations are shown for patients in whom a new injection was performed (light green box plot) and for patients in whom a new injection was not performed (end of the therapy, trough level too high) (dark green box plot). The black line shows the targeted peak (60 mg/L). (B) Distribution of patients receiving amikacin and patients in whom a new peak was not measured [end of treatment (TT), high trough, no blood sample]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 4.** (A) Course of dosing, and peak and trough plasma concentrations of gentamicin according to the day of therapy. Dosing is shown in blue box plot and peak plasma concentrations in the white box plot. Trough plasma concentrations are shown for patients in whom a new injection was performed (light green box plot) and for patients in whom a new injection was not performed (end of the therapy, trough concentration too high) (dark green box plot). The black line shows the targeted peak (30 mg/L). (B) Distribution of patients receiving gentamicin and patients in whom a new peak concentration was not measured [end of treatment (TT), high trough, no blood sample]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

were monitored, dose changes were not commonly performed, leading to adequate  $C_{max}$  being observed in only 25% of patients with amikacin therapy and in none of the patients receiving gentamicin therapy.

The present study was performed in a French ICU that could be considered as broadly representative of southern French ICUs [25]. The sources of infection and the most frequent pathogens are similar to previous studies [1,26,27]. In our unit, we give aminoglycosides as part of broad empirical anti-infective therapy in order to increase the probability of appropriate pathogen coverage [3]. In this context, gentamicin is usually given in community-acquired infection when a Gram-positive pathogen is suspected. Amikacin is usually given when a Gram-negative pathogen is suspected, especially in cases of nosocomial infection. Regarding aminoglycoside sampling, some bloods were not withdrawn in line with the protocol (34/40 non-included patients). In a recent study reported by de Montmollin et al., 36/67 episodes of amikacin administration had incorrect or no measurement of  $C_{max}$  [15].

In contrast to the two previous studies reported by Taccone et al. [17] and de Montmollin et al. [15], no regimen of high initial dose of aminoglycoside was recommended. Therefore, the present study tests the daily practice of aminoglycoside prescription on the basis of 15 mg/kg for amikacin and 3 mg/kg for gentamicin. The mean initial doses of amikacin and gentamicin were  $22.6 \pm 6.9$  mg/kg [corresponding to a dosing ratio (given dose/recommended minimal dose) of  $1.50 \pm 0.46$ ] and  $6.6 \pm 2.3$  mg/kg (corresponding to a dosing ratio of  $2.20 \pm 0.76$ ), respectively. These results show that physicians applied usual recommendations for high doses

of antibiotics in the ICU. Despite the use of such theoretical high doses, the initial infusion led to only 4% and 24% of patients having an adequate  $C_{max}$  with gentamicin and amikacin, respectively.

The proportion of patients with an adequate  $C_{max}$  with amikacin is far less than that reported by Taccone et al. [17] and de Montmollin et al. [15] who used higher initial doses of amikacin (25 mg/kg) leading to approximately two-thirds of patients having adequate  $C_{max}$ . In a randomised trial, Gálvez et al. [16] compared three initial doses of amikacin (15, 25 and 30 mg/kg). They reported that a targeted  $C_{max}$  of  $>60$  mg/L was more easily reached in patients given 30 mg/kg (76% of patients). In critically ill haematological malignancy patients with infection requiring aminoglycoside therapy, Blackburn et al. [28] recently reported a median first dose of tobramycin and amikacin of 5.8 mg/kg and 13.8 mg/kg, respectively. As in the present study, the authors reported only 25% achievement of adequate first  $C_{max}$  even with lower target concentrations (tobramycin 20 mg/L and amikacin 40 mg/L).

To the best of our knowledge, few studies have focused on the concentrations of aminoglycosides throughout the course of therapy in ICU patients. In contrast to the two previous studies, we performed an audit of two agents, amikacin and gentamicin, to describe how target concentration achievement changed with time. First, even though the mean initial dose of gentamicin was nearly two-fold the minimum recommended dose ( $6.6 \pm 2.3$  mg/kg), an adequate  $C_{max}$  was reached in only 1 of 24 patients on Day 1. For amikacin, an initial mean dose of  $22.6 \pm 6.9$  mg/kg led to an adequate first  $C_{max}$  in only 16/66 patients (24%). Second, the clinical practice of aminoglycoside therapy

appears to be very heterogeneous for the duration of treatment (2–5 days).

Moreover,  $C_{\max}$  and  $C_{\min}$  were not systematically measured on subsequent days. When the monitoring of  $C_{\max}$  of amikacin and gentamicin was performed, it led to a change in dosing of amikacin and gentamicin in only 14/50 and 13/23 patients given amikacin and gentamicin, respectively. In these patients with dosing adjustment, the targeted  $C_{\max}$  was only achieved in 2 patients given amikacin and none of the patients given gentamicin.

The lack of adherence to the French dosing guideline in this study highlights the difficulty in implementing dosing recommendations in clinical daily practice [14,29]. However, this evaluation should help improve local practice: first, by using higher doses of gentamicin or amikacin; second, by being rigorous for peak and trough concentration assessments; and third, by adjusting doses according to measured peak concentrations.

This is probably a hard objective to reach, as many barriers exist for implementing recommendations [30]. Indeed, some physicians could be reluctant to give high doses of aminoglycosides in patients at risk of renal insufficiency. Some of them did not probably know the recommendation to give the highest dose of aminoglycosides in patients with a suspected increased volume of distribution such as ICU patients [14,20]. Interestingly, Taccone et al. [17] and de Montmollin et al. [15] proposed to give 25 mg/kg of total body weight. Therefore, many efforts are required for optimising aminoglycoside administration. Moreover, as the targeted peak levels have been determined according to the worst (highest) MIC, some doses were probably efficient with a favourable patient outcome making the physician reluctant to use higher doses on subsequent days.

The lack of achievement of  $C_{\max}$  should bring into question current dosing recommendations and the potential to lead to clinical failure or the emergence of resistant pathogens [9]. Moreover, the present study highlights the importance of the first dose as subsequent doses were rarely adapted and, when adapted, the dosing rarely led to adequate peak plasma levels.

In addition to low initial dosing, the findings of the present study could be explained by the altered pharmacokinetics of aminoglycosides in ICU patients. In such patients, alterations in the volume of distribution and creatinine clearance could lead to decreased  $C_{\max}$  and explain the low proportion of patients with adequate  $C_{\max}$  in the present study [20]. However, of concern, the multivariate analysis did not isolate any factor associated with low  $C_{\max}$ . This result was the same as that observed by Taccone et al. [17] but not by de Montmollin et al. [15] who found that a positive 24-h fluid balance was associated with lower  $C_{\max}$ .

The present study has some limitations. First, only gentamicin and amikacin were surveyed and we cannot extrapolate the findings to other aminoglycosides. Second, some factors that could alter the pharmacokinetics of aminoglycosides were not analysed (albumin, creatinine clearance) [20]. Third, we assumed that adequate  $C_{\max}$  were 60 mg/L and 30 mg/L, which are the targets recommended by current dosing guidelines that take into account the highest MIC of susceptible pathogens [14]. As the MIC of the pathogen was not determined in this study, we can suspect that some  $C_{\max}$  values were adequate for clinical treatment ( $8\text{--}10 \times \text{MIC}$ ). Moreover, aminoglycosides are always co-administered with another antibiotic to extend the spectrum of initial antibiotic therapy, and the additive/synergistic effects of the second antibiotic could reduce the impact of not achieving an adequate first  $C_{\max}$ . However, our approach is pragmatic and representative of contemporary approaches to aminoglycoside dosing. Finally, we did not observe a difference in patient outcome with an increasing magnitude of the first  $C_{\max}$ , in contrast to the findings reported by Moore et al. [8,9]. This could be explained by differences in recruited patients (Moore et al., bacteraemia, 100% culture-positive microbiology versus this study, severe

sepsis, 72% culture-positive microbiology) and the differences in the targeted  $C_{\max}$  (two-fold lower in Moore's studies). The current study was also not powered for showing a difference in mortality rate, although such a study is certainly suggested.

In clinical practice, the present study confirms the data reported by Taccone et al. [17] and de Montmollin et al. [15] that contemporary recommended doses of aminoglycosides do not reliably achieve contemporary recommended target peak concentrations. These results support the use of higher doses of aminoglycosides in ICU patients (amikacin 30 mg/kg or gentamicin 8 mg/kg). Such dosing would be valuable particularly when risk factors of low peak plasma concentrations are present (i.e. positive fluid balance, increased creatinine clearance, high cardiac output, systemic inflammation response syndrome) [14]. Moreover, the present study shows that monitoring  $C_{\max}$  should be better implemented and could lead to adapting the aminoglycoside dosing in order to avoid too low  $C_{\max}$  that could be associated with inefficient therapy. Monitoring of peak and trough plasma concentrations should help the physician to achieve adequate therapy throughout the course of treatment. Further studies must be performed to assess such a strategy. All of these objectives required efforts from each physician (for knowing and applying recommendations) and from each institution and scientific societies (for divulging and helping the implementation of good clinical practices) [30].

## 5. Conclusion

The present study showed that standard dosing of amikacin or gentamicin led to adequate  $C_{\max}$  in only 19% of patients. A first insufficient dose is associated with subsequent subtherapeutic doses. This emphasises the importance of the first dose to detect a subtherapeutic regimen and potentially adapt the following doses. This brings into question the appropriateness of current dosing recommendations and supports the initiation of aminoglycoside therapy with higher doses in ICU patients with severe sepsis.

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## Competing interests

None declared.

## Ethical approval

As this was a non-interventional study to assess the daily practice of aminoglycoside monitoring in the ICU of Nîmes University Hospital (Nîmes, France), approval by the Comité de Protection des Personnes was not required according to French law. Therefore, the study was approved by the Institutional Review Board of Nîmes University Hospital [IRB 13/10-02] and was declared to the Commission nationale de l'informatique et liberté [CNIL # 1713434]. For this reason, the need for written informed consent from patients was waived. However, all patients and/or their next of kin were verbally informed of the data collection and could refuse to participate.

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**Article 2 : Impact des fortes posologies d'aminosides (30 mg/kg pour l'amikacine et 8 mg/kg pour la gentamicine) sur les concentrations plasmatiques maximales d'aminosides au cours du sepsis.**

Dans ce travail, 63 patients en choc septique recevant une dose d'amikacine (n=47) ou de gentamicine (n=16) ont été inclus. La dose de 30 mg/kg pour l'amikacine et 8 mg/kg pour la gentamicine était calculée à partir du poids dit « adapté », soit le poids réel pour les patients avec un indice de masse corporelle (IMC)  $\leq 30$  kg/m<sup>2</sup> et le poids ajusté (poids idéal théorique + 0,43 x (poids réel – poids idéal théorique)) pour les patients avec un IMC >30 kg/m<sup>2</sup>. L'augmentation des posologies d'aminosides ont permis d'augmenter la proportion de patients (n=36, 77%) présentant des concentrations plasmatiques d'amikacine dans la cible thérapeutique (>60 mg/L). Le Vd calculé par une méthode non compartimentale était de  $0,43 \pm 0,17$  L/kg, confirmant l'augmentation du Vd dans la population septique comparée à la population de volontaires sains. Lorsque la CMI des pathogènes responsables de l'infection était mesurée (n=16), le ratio  $C_{\max}/CMI \geq 10$  était atteint dans plus de 90% des cas. La prise en compte de l'écologie locale pourrait permettre l'utilisation de posologies plus faibles, toutefois cette approche nécessite une mesure rapide de la CMI et un monitoring des taux plasmatiques d'aminosides en routine.

Dans ce travail, l'utilisation de fortes posologies d'aminosides était associée à une concentration résiduelle supérieure au taux recommandé de 2,5 mg/L pour l'amikacine et 0,5 mg/L pour la gentamicine dans plus de la moitié des cas (n=23 et 56, respectivement) ayant pour conséquence l'absence de réinjection de dose au deuxième jour de traitement. Ces concentrations résiduelles hautes à J1 étaient observées en dehors de toute insuffisance rénale aiguë suggérant une diminution des mécanismes d'élimination de ces antibiotiques mal corrélée aux marqueurs de dysfonction rénale utilisée en réanimation.

**Conclusion :** Ce travail pose de nombreuses questions sur le schéma optimal d'administration des aminosides dans le contexte de choc septique. Il est nécessaire de trouver un compromis entre l'obtention de  $C_{max}$  efficaces et la limitation de la toxicité rénale liée à des concentrations résiduelles trop élevées. De plus, l'espacement des réinjections de doses pourrait conduire à une inefficacité thérapeutique et/ou à une exposition *in fine* plus prolongée aux aminosides. En effet, la toxicité rénale des aminosides est un phénomène saturable qui a été principalement démontré pour des traitements prolongés.<sup>42,43</sup>

Article 2 : Impact des fortes posologies d'aminosides (30 mg/kg pour l'amikacine et 8 mg/kg pour la gentamicine) sur les concentrations plasmatiques maximales d'aminosides au cours du sepsis. *JAC, rang A, impact factor 2015 : 5.071.*<sup>44</sup>

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Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis

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**Objectives:** Low first-dose peak serum concentrations of amikacin and gentamicin are commonly reported in ICU patients. The present study aimed to assess whether 30 mg/kg amikacin or 8 mg/kg gentamicin achieved target concentrations in ICU patients with severe sepsis.

**Patients and methods:** Sixty-three ICU patients (Simplified Acute Physiology Score II = 43 ± 16) with severe sepsis and an indication for intravenous amikacin (n = 47) or gentamicin (n = 16) were included. The first (30 mg/kg amikacin; 8 mg/kg gentamicin) and subsequent doses and corresponding peak concentrations (30 min after the completion of an infusion) were recorded. French guideline target concentrations were ≥ 60 and ≥ 30 mg/L for amikacin and gentamicin, respectively. A target pharmacokinetic/pharmacodynamic ratio of 10 × MIC was also measured.

**Results:** Pulmonary, abdominal and urinary tract infections were diagnosed in 56 patients. Infection was confirmed in 37 patients (59%). The targeted first-dose peak concentration was achieved in 37/63 patients (59%) [amikacin 36/47 (77%) and gentamicin 1/16 (6%)], and 59/63 patients (94%) achieved the pharmacokinetic/pharmacodynamic ratio using the MIC data that were available from 21 patients. However, the second dose of aminoglycoside was withheld because of high trough concentrations in nearly half of patients who did not have renal dysfunction.

**Conclusions:** In this study, 30 mg/kg amikacin and 8 mg/kg gentamicin led to target peak serum concentrations in 59% of patients.

Introduction

In patients with severe sepsis, aminoglycosides are often given as part of empirical broad-spectrum anti-infective therapy.<sup>1-5</sup> Serum concentrations are used as a surrogate of tissue concentration to assess the appropriateness of dosing and anti-infective exposure. Maximal antibacterial activity is considered to occur when the ratio of the peak concentration to MIC for the infective pathogen (peak/MIC) is 8-10 × greater than the MIC.<sup>6,7</sup> Recent recommendations suggest target peak concentrations of 30-40 mg/L for gentamicin and 60-80 mg/L for amikacin (EUCAST).<sup>8-10</sup> Standard doses of aminoglycosides are associated with low peak concentrations,<sup>11,12</sup> in contrast to those of higher doses of amikacin.<sup>9,10</sup>

The alterations of pharmacokinetic characteristics can explain the difficulty in reaching adequate peak concentrations in ICU patients.<sup>10,13</sup>

In order to improve the achievement of target peak concentrations, either 30 mg/kg amikacin or 8 mg/kg gentamicin was prescribed in ICU patients with severe sepsis.<sup>8</sup> The aim of the present study was to report the rate of achievement of target peak concentrations using these doses.

Patients and methods

The Institutional Review Board approved this observational study. According to French law, patient written informed consent was waived.

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However, patients or their surrogates were verbally informed and could refuse to participate.

From 27 October 2014 to 28 February 2015, ICU patients with severe sepsis treated with aminoglycosides were recruited. We excluded patients who were <18 years of age, who required renal replacement therapy (RRT), who had an allergy to aminoglycosides, who were confirmed and/or suspected to have myasthenia and/or ICU-acquired neuromuscular disorder, who were under guardianship or who were prisoners. No patient was included more than once in the data collection.

In combination with broad-spectrum antibiotics, according to the suspected pathogens and local clinical practice, 30 mg/kg amikacin or 8 mg/kg gentamicin was given (30 min intravenous infusion; the dosage ampoule was systematically emptied with a 5 mL flush). The weight metric used in this study was called an adapted body weight (ABW), which was determined as follows:

For BMI  $\leq 30$  kg/m<sup>2</sup>, ABW = total body weight (TBW)

For BMI  $> 30$  kg/m<sup>2</sup>, ABW = ideal body weight (IBW)  
+ 0.43(TBW – IBW)

IBW was calculated according to the Lorenz formula:

IBW = height (cm) – 100 – [(height(cm) – 150)]/X,  
X = 4 for males and X = 2.5 for females

The peak serum concentration sampling occurred 30 min after the end of the infusion. Subsequent trough and peak concentrations were withdrawn as part of unit practice.

The targeted concentrations for amikacin and gentamicin were: amikacin, peak  $\geq 60$  mg/L and trough  $< 2.5$  mg/L; and gentamicin, peak  $\geq 30$  mg/L and trough  $< 0.5$  mg/L.<sup>8</sup>

Patient characteristics, medical history and Simplified Acute Physiology Score II (SAPS II) were collected at admission.<sup>14</sup> During each patient's ICU stay, the SOFA<sup>15</sup> score and the Acute Kidney Injury Network (AKIN)<sup>16</sup> score were recorded daily. The need for RRT and co-prescription of nephrotoxins (e.g. glycopeptides, diuretics) was recorded.

Type of infection and antibiotics given were recorded, and microbiological cultures were collected. Genus and species were determined using the MALDI-TOF technology Vitek MS (bioMérieux, Marcy-l'Étoile, France). Vitek2 (bioMérieux) was used to determine antibiotic susceptibilities. The MICs of aminoglycosides were determined using the Etest method (bioMérieux). Isolates were classified as susceptible (S), intermediate (I) or resistant (R) to the antibiotics according to the EUCAST breakpoints. When the MIC was not available, the susceptibility breakpoint MICs of amikacin and gentamicin were used to determine the local extrapolated target peak, defined as  $10 \times$  highest MIC.<sup>7</sup>

The volume of distribution (V) was defined as first dose (mg/kg)/first serum peak (mg/L).

Amikacin and gentamicin concentrations were measured using automated immunoassays (Roche Diagnostics GmbH Mannheim) using a cobas c system.<sup>12</sup> The limits of quantification were 0.8 mg/L and 0.3 mg/L for amikacin and gentamicin, respectively.

### Statistical analysis

We recently reported an achievement of target peak serum concentration in 19% of patients.<sup>12</sup> The present study was aimed at demonstrating that 30 mg/kg amikacin and 8 mg/kg gentamicin would lead to the achievement of a target level in 70% of patients as previously reported.<sup>9,10</sup> In order to determine whether the new regimens would increase the rate to 70% with  $\alpha$  and  $\beta$  risks of 0.05 and 0.1, respectively, 14 patients would need to be included per aminoglycoside.

Data are expressed as mean  $\pm$  SD or median (IQR) for quantitative variables according to the normality of their distribution. Qualitative data are

expressed as absolute values with percentages. For comparisons, the  $\chi^2$  test, Student's t-test and Mann-Whitney U-test were performed.  $P < 0.05$  was considered significant.

## Results

### Patients, infections and pathogens

Aminoglycosides were administered to 166 of 404 admitted patients. For 103 of the patients who received aminoglycosides,

**Table 1.** Included patients, types of infection and pathogens

Patients (male/female), n (n/n)	63 (39/24)
Patients given amikacin/gentamicin, n/n	47/16
Age (years), mean $\pm$ SD	68 $\pm$ 16
Height (cm), mean $\pm$ SD	168 $\pm$ 8
Total body weight at admission (kg), mean $\pm$ SD	75 $\pm$ 22
BMI at admission (kg/m <sup>2</sup> ), mean $\pm$ SD	26.5 $\pm$ 7.6
Patients with BMI $\geq 30$ kg/m <sup>2</sup> , n (%)	19 (30)
IBW (kg), mean $\pm$ SD	63 $\pm$ 6
ABW (kg), mean $\pm$ SD	68 $\pm$ 11
SAPS II at admission, mean $\pm$ SD (median)	43 $\pm$ 16 (39)
Creatinine plasma concentration at admission ( $\mu$ mol/L), mean $\pm$ SD	100 $\pm$ 52
Albumin plasma concentration at admission (g/L) (n=48), mean $\pm$ SD	32 $\pm$ 6
SOFA at the initiation of aminoglycoside therapy, median (IQR)	7 (4–10)
AKIN at the initiation of aminoglycoside therapy, median (IQR)	0 (0–1)
Death in ICU, n (%)	16 (25)
Death in hospital (prior to discharge), n (%)	17 (27)
Type of infection, n	
pulmonary	40
abdominal	7
urinary tract	9
septicaemia	5
others	2
Isolated pathogen, n	
<i>Staphylococcus aureus</i>	6
<i>Staphylococcus</i> spp.	2
<i>Enterococcus</i> spp.	3
<i>Haemophilus influenzae</i>	2
<i>Escherichia coli</i>	14
<i>Klebsiella pneumoniae</i>	3
<i>Proteus mirabilis</i>	2
<i>Enterobacter</i> spp.	6
<i>Serratia marcescens</i>	1
<i>Pseudomonas aeruginosa</i>	2
<i>Candida</i> spp.	8
others	7
Patients with no isolated pathogen, n (%)	26 (41)
Patients with only 1 isolated pathogen, n (%)	15 (24)
Patients with $> 1$ isolated pathogen, n (%)	22 (35)
Patients with MIC, n (%)	21 (33)
MIC of amikacin (mg/L), median (range)	$\leq 2$ ( $\leq 2$ to $\leq 4$ )
MIC of gentamicin (mg/L), median (range)	$\leq 1$ ( $\leq 0.5$ to $\leq 1$ )

first peak concentrations were not available, leading to the inclusion of 63 patients in the study (Table 1). Types of infection and pathogens are shown in Table 1. The highest MICs of amikacin and gentamicin were  $\leq 4$  and  $\leq 1$  mg/L, respectively.

**Efficiency of the first dose**

Thirty-seven patients (59%) had a first peak concentration above the recommended target (Figure 1a and b).

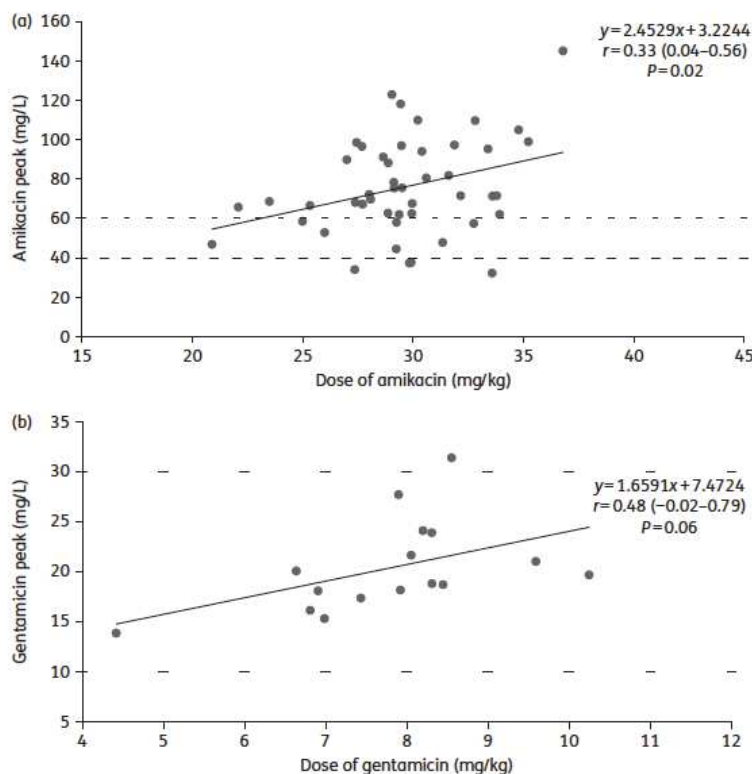
**Amikacin therapy (47 patients)**

Of the 47 patients who received amikacin, 36 patients (77%) had a peak concentration  $>60$  mg/L (Figure 1a). The mean first dose was  $29.6 \pm 3.3$  mg/kg ABW. The mean peak serum concentration was  $75.8 \pm 24.5$  mg/L, corresponding to a V of  $0.43 \pm 0.17$  L/kg. A dose  $\geq 30$  mg/kg would lead to 90% of the studied population achieving the targeted peak. The first peak was greater than  $10 \times \text{MIC}$  (4 mg/L) in 15/16 patients with measured MIC. When this MIC was extrapolated to all patients, 43/47 (91%) first

peaks were  $>10 \times \text{MIC}$ . A trough concentration  $\geq 2.5$  mg/L was reported in 23/47 (49%), 12/20 (60%) and 9/15 (60%) patients on days 2, 3 and 4, respectively, leading to withholding of the subsequent dose. Serum creatinine concentrations remained stable throughout amikacin therapy. Four patients required RRT, which was considered to be related to severe sepsis.

**Gentamicin therapy (16 patients)**

Of the 16 patients who received gentamicin, only one patient (6%) had a peak concentration  $>30$  mg/L (Figure 1b). The mean first dose of gentamicin was  $7.8 \pm 1.3$  mg/kg ABW. The mean first peak serum concentration was  $20.4 \pm 4.6$  mg/L. The calculated V was  $0.39 \pm 0.07$  L/kg. A dose  $\geq 9$  mg/kg would lead to 90% of the studied population achieving the targeted peak. The first peak was greater than  $10 \times \text{MIC}$  (1 mg/L) in 5/5 patients with measured MIC. When this MIC was extrapolated to all patients, all first peak concentrations were greater than  $10 \times \text{MIC}$ . A trough concentration  $\geq 0.5$  mg/L was reported in 9/16 (56%), 6/7 (86%) and 3/6 (50%) patients on days 2, 3 and 4, respectively, leading to



**Figure 1.** Observed and target peak serum concentrations of amikacin (a) or gentamicin (b). (a) Amikacin peak concentrations after the first dose with target concentrations according to EUCAST (60 mg/L) and local extrapolated target peak according to MIC data (40 mg/L). (b) Gentamicin peak concentrations after the first dose with target concentrations according to EUCAST (30 mg/L) and local extrapolated target peak according to MIC data (10 mg/L). Peak concentrations, filled circles; EUCAST target, upper broken line; local extrapolated target, lower broken line; correlation line, continuous line.

withholding of the subsequent dose. Serum creatinine concentrations remained stable throughout gentamicin therapy.

## Discussion

In the present study, a first dose of 30 mg/kg amikacin or 8 mg/kg gentamicin led to achievement of targeted peak concentrations in 59% of patients (77% of patients given amikacin and 6% given gentamicin). This dosing was associated with high trough concentrations, which led to withholding of the subsequent dose in nearly half of patients on day 2 of treatment. No acute kidney injury related solely to aminoglycoside use was observed.

The doses of 30 mg/kg amikacin and 8 mg/kg gentamicin are recommended in patients with suspected increased  $V_d$  as seen in ICU patients.<sup>8</sup> The present study included patients similar to those included in previous studies of severe sepsis.<sup>9–11,17–19</sup> The magnitude of the first serum peak concentration of amikacin or gentamicin was similar to that reported in studies calculating the dosing from actual body weight.<sup>9,10,19</sup> The use of such dosing led to an increase in the rate of achievement of target peak concentrations from 24% to 77% after the first dose.<sup>1,2</sup>

In contrast to these previous studies, this study also recorded the peak and trough concentrations over the entire course of aminoglycoside treatment. With these high doses, nearly half of patients were not given a subsequent dose, because their trough concentration was above guideline recommendations, potentially exposing these patients to a greater risk of nephrotoxicity.<sup>6</sup> However, no impairment in renal function related to the use of aminoglycosides was observed. This finding could question the monitoring of trough concentrations when high doses of aminoglycosides are used, although clinicians were careful to withhold doses if high trough concentrations were observed, which may have reduced the development of nephrotoxicity. When taking into account data of the measured MICs, we found that nearly all patients reached the targeted peak aminoglycoside concentration after the first dose. In this context, knowledge of the local susceptibility patterns could allow more-accurate monitoring and lower dosing. This hypothesis is yet to be tested. Some limitations of this study should be declared. First, many patients had no monitoring of the first peak. This fact should lead us to reinforce the importance of adhering to the guidelines for aminoglycoside monitoring in our unit. Second, aminoglycosides are frequently co-administered with another antibiotic to extend the spectrum of initial antibiotic therapy, and the additive/synergistic effects of the second antibiotic are not measurable *in vivo*.<sup>20</sup> This factor could reduce the clinical consequences of not achieving the targeted first peak concentration. Third, the present study was not designed to measure the impact of these doses on patient outcome or on renal function.

## Conclusions

Doses of 30 mg/kg amikacin or 8 mg/kg gentamicin led to targeted peak concentrations in 59% of patients, but they led to high trough concentrations in more than 50% of patients.

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## Transparency declarations

None to declare.

## Author contributions

C. R. participated in the design of the study, collecting patient data, analysing the data and writing the paper. B. N. participated in collecting patient data, analysing the data and writing the paper. B. L. participated in the design of the study, performing the statistical analysis, analysing the data and writing the paper. A. F. participated in the design of the study, analysing the data and writing the paper. H. K. participated in collecting patient data. A. E. participated in the design of the study and analysing the data. J.-P. L. participated in the design of the study, performing bacteriological analysis and analysing the bacteriological data. B. A. participated in the design of the study, analysing the data and writing the paper. J.-Y. L. participated in the design of the study, collecting patient data, analysing the data and writing the paper. J. A. R. participated in the design of the study, analysing the data and writing and revising the paper. L. M. participated in the design of the study, collecting patient data, analysing the data and writing the paper. All authors read and approved the final manuscript.

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### ***b) Altération de la liaison protéique***

La deuxième conséquence observée lors du sepsis est la survenue fréquente d'une hypoalbuminémie profonde.<sup>45</sup> L'albumine est la principale protéine à laquelle se lie les antibiotiques, la deuxième protéine liant principalement les molécules basiques est l'alpha-1-glycoprotéine acide. Classiquement, on distingue la fraction liée aux protéines de la fraction libre, seule fraction diffusant aux tissus, agissant sur le site d'action et pouvant être éliminée ou métabolisée. La fraction liée aux protéines est considérée comme une forme de stockage et/ou de transport de l'antibiotique. Par ailleurs, l'albumine joue un rôle essentiel dans le maintien de la pression oncotique qui génère un gradient favorisant le passage de liquide du secteur interstitiel vers le secteur intravasculaire.

Par conséquent, une diminution des concentrations plasmatiques d'albumine va donc entraîner :

- une diminution de la fraction d'antibiotiques liée aux protéines et par conséquent une augmentation de la fraction libre responsable de l'effet thérapeutique des antibiotiques,
- une diminution de la pression oncotique qui va aggraver la fuite de liquide vers le secteur interstitiel et donc augmenter le Vd des antibiotiques.

Cette altération liée au sepsis va principalement affecter les antibiotiques présentant une liaison protéique forte tels que le ceftriaxone, la teicoplanine, l'oxacilline, la céfazoline.<sup>46-</sup>

50

Afin d'évaluer l'impact de la liaison protéique, nous avons développé un modèle PK de population permettant d'estimer simultanément les concentrations plasmatiques totales et libres de ceftriaxone dans une population de patients en choc septique. Cette étude, n'ayant pas encore été soumise, ne sera donc pas présentée dans ce travail de thèse.

### ***c) Modifications de l'élimination des antibiotiques***

Trois cas de figures peuvent être observés au cours du sepsis.

- Dans le premier cas de figure, le sepsis est associé à un état hyperdynamique (le plus souvent à la phase initiale du choc septique), lui-même associé à une augmentation de la clairance des antibiotiques pouvant exposer à un risque de sous-dosage plasmatique.<sup>51-53</sup>
- Dans le deuxième cas de figure, le sepsis peut évoluer vers un état de choc septique dès lors qu'apparaissent des défaillances d'organes. L'atteinte microcirculatoire septique se traduit par l'existence de micro-thrombi dans les capillaires qui vont entraîner une raréfaction et une diminution de la densité fonctionnelle capillaire à l'origine de ces défaillances d'organes.<sup>37,38</sup> Les principales défaillances conduisant à une modification de la clairance des antibiotiques sont la dysfonction rénale et la dysfonction hépatique. Les antibiotiques hydrophiles sont majoritairement éliminés par voie rénale. Une diminution significative de la clairance rénale des antibiotiques augmente leur demi-vie exposant les patients à un risque de surdosage et de potentielle accumulation et/ou toxicité. Les antibiotiques lipophiles, majoritairement métabolisés par le foie vont voir leur PK affectée par une diminution significative de la fonction hépatique.
- Dans le troisième cas de figure, la sévérité de la dysfonction d'organe (rénale ou hépatique) nécessite la mise en place d'une suppléance d'organe telle que l'EER qui va générer une clairance extra-corporelle de l'antibiotique variant avec le type d'EER utilisé. **Articles 3, 4, 5 et 6.**

#### *d) Variabilité inter-individuelle*

La grande majorité des études PK s'intéressant à la population de réanimation rapporte une variabilité inter-individuelle des concentrations plasmatiques d'antibiotiques majeure.<sup>9,12</sup>

Cette variabilité inter-individuelle s'explique en partie par le degré de sévérité du sepsis et des défaillances d'organe. D'autres facteurs tels que le poids et l'âge peuvent également influencer la PK des antibiotiques dans cette population. L'étude multicentrique, internationale, DALI a mis en évidence cette grande variabilité des concentrations plasmatiques observées pour les bêta lactamines chez les patients de réanimation.<sup>9</sup> En raison de cette large variabilité inter-individuelle, de nombreux experts en PK/PD ont pointé du doigt la nécessité de monitorer les taux plasmatiques d'antibiotiques afin d'optimiser leur utilisation. Toutefois, à ce jour, aucune étude n'a démontré un bénéfice en terme de survie de cette approche individualisée.

#### ***4. ALTERATIONS DE LA PHARMACOCINETIQUE DES ANTIBIOTIQUES INDUITES PAR L'EPURATION EXTRA-RENALE***

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##### ***a) Type d'EER utilisée***

La défaillance rénale au cours du sepsis va nécessiter le recours à l'EER dans 70% des cas.<sup>4</sup> Deux grands types de techniques d'EER peuvent être appliquées : continues ou intermittentes. Les techniques continues sont privilégiées chez les patients de réanimation pour leur meilleure stabilité hémodynamique.<sup>54,55</sup> L'EER fait appel à deux principes d'épuration : la convection (représentée par l'hémofiltration) pour laquelle les échanges sont gouvernés par un gradient de pression et la diffusion (représentée par l'hémodialyse) pour laquelle les échanges sont gouvernés par un gradient de concentration. Ces deux principes peuvent être couplés dans les techniques d'hémodiafiltration.

Selon la technique appliquée, l'élimination d'antibiotiques induite par cette technique peut largement varier expliquant en partie la variabilité des concentrations plasmatiques d'antibiotiques observées chez les patients septiques sous EER.<sup>56</sup> L'utilisation de doses

conventionnelles d'antibiotiques dans cette population expose au risque de sur ou sous dosage. La méta-analyse réalisée par Seyler et al., rapporte des concentrations plasmatiques d'antibiotiques inadéquates dans 30 à 60 % des cas selon la bêta-lactamine considérée.<sup>57</sup>

Dans ce contexte, définir la posologie optimale d'antibiotiques pour cette population se révèle être un vrai challenge.<sup>58</sup> Plusieurs études et méta-analyses ont tenté d'apporter des réponses à cette problématique.<sup>12,59,60</sup> Une large étude multicentrique internationale menée par Roberts et al. A laquelle notre équipe a pris part, devrait être à l'origine de recommandations de doses selon le type de technique, l'intensité et le type de membrane utilisée pour les beta-lactamines (pipéracilline-tazobactam, méropénème) et les glycopeptides (vancomycine).<sup>61</sup>

L'analyse PK de population est une autre approche permettant de caractériser une population PK particulière, dans ce travail de thèse la population de patients de réanimation sous EERc, et de définir des schémas posologiques plus adaptés à l'aide de simulations de Monte Carlo. Cette approche est détaillée dans le chapitre 5.2.

### ***b) Paramètres d'EER appliqués***

Une fois la technique d'EER choisie (intermittente/continue, hémofiltration/hémodialyse/hémodiafiltration), les paramètres pouvant faire varier la clairance extra-corporelle de l'antibiotique sont nombreux<sup>25,59,60,62,63</sup> :

- liés au réglage de l'EER : intensité de l'EER, pré ou post dilution, débit sanguin machine, le type de membrane utilisé, la durée de vie de la membrane,<sup>64,65</sup>
- lié à la nature de l'antibiotique : poids moléculaire, liaison protéique, caractère lipo ou hydrophile, charge moléculaire, capacité d'adsorption,<sup>66</sup>
- lié au patient : volémie, clairance rénale résiduelle.<sup>67</sup>



-En théorie, l'hémodialyse va principalement épurer les petites molécules et dépend de la concentration de ces molécules dans le secteur plasmatique tandis que l'hémofiltration va épurer les petites et moyennes molécules indépendamment de leur concentration dans le secteur plasmatique. Toutefois, considérant que la taille des pores de la membrane utilisée va être le principal élément déterminant du passage transmembranaire des molécules en EER et que cette taille est largement supérieure (20 à 30 000 Da) au poids moléculaire de la majorité des antibiotiques, la technique d'EER n'a, en théorie, que peu d'influence.

-La liaison protéique est un autre facteur influençant la clairance d'antibiotiques induite par l'EER. Seule la forme libre, non liée aux protéines peut être épurée à travers la membrane. Les antibiotiques fortement liés aux protéines vont donc être peu épurés par l'EER. Néanmoins, des variations importantes de la fraction libre de ces antibiotiques liées à une hypoalbuminémie vont entraîner une augmentation de la clairance de ces molécules par l'EER et entraîner des perturbations majeures de ces antibiotiques.

## 5. METHODES D'ANALYSE PHARMACOCINETIQUE

Le grand nombre de facteurs rentrant en compte dans la PK des antibiotiques dans la population de patients en choc septique rend donc l'analyse de l'influence de l'EER complexe. Plusieurs approches PK peuvent être utilisées afin de déterminer la nécessité ou non d'adapter les posologies d'antibiotiques chez les patients septiques sous EER.

### *a) Approche mécanistique*

L'approche mécanistique a longtemps été utilisée pour estimer la quantité d'antibiotique épurée par la membrane d'EER. Elle se base sur la mesure des concentrations d'antibiotiques dans le plasma et dans l'effluent.

Le calcul de la clairance d'antibiotique induite par l'EER va dépendre de la technique utilisée :

- Méthode convective

La clairance induite par l'hémofiltration continue va dépendre du **coefficient de partage** (**S<sub>c</sub>**, **Sieving coefficient en anglais**) propre à chaque molécule et qui représente la capacité de cette molécule à traverser la membrane d'EER.

La formule du S<sub>c</sub> est la suivante :

$$\frac{[\text{antibiotique}]_{\text{ultrafiltrat}}}{[\text{antibiotique}]_{\text{plasma}}}$$

Le principal déterminant de S<sub>c</sub> est la fixation protéique. Ce coefficient va varier, en théorie, de 0 (aucune élimination par la membrane d'EER) à 1 (élimination totale par l'EER).

Le calcul de la clairance doit également prendre en compte le mode de restitution de fluide appliqué : pré- ou post-dilution.<sup>68,69</sup>

- En post-dilution, la clairance de l'antibiotique dépend du S<sub>c</sub> et du **débit d'ultrafiltrat** (**Q<sub>UF</sub>**) :

$$Cl_{\text{post-CVVHF}} = S_c \times Q_{\text{UF}}$$

- En pré-dilution, la clairance de l'antibiotique est affectée par la dilution induite par la restitution de fluide en amont de la membrane d'EER. La clairance des molécules en hémofiltration continue en pré-dilution est corrigée selon la formule suivante :

$$Cl_{\text{pre-CVVHF}} = S_c \times Q_{\text{UF}} \times Q_s / (Q_s + Q_{\text{pre}})$$

Toutefois, la clairance de l'antibiotique ne sera significativement altérée que lorsque des Q<sub>UF</sub> importants seront appliqués.<sup>69</sup>

- Méthode diffusive

La clairance de l'antibiotique en hémodialyse continue va dépendre du **coefficient de saturation (S<sub>d</sub>)** défini comme :

$$\frac{[\text{Antibiotique}]_{\text{dialysat}}}{[\text{Antibiotique}]_{\text{plasma}}}$$

Le principal déterminant de S<sub>d</sub> est une fois encore la fixation protéique.

La clairance de l'antibiotique en hémodialyse continue va être sous la dépendance du débit de dialysat (Q<sub>d</sub>) et du coefficient de saturation :

$$Cl_{\text{CVVHD}} = Q_d \times S_d$$

- Méthode associant convection et diffusion

En hémofiltration continue, la clairance de l'antibiotique est estimée comme suit :

$$Cl_{\text{CVVHDF}} = (Q_{\text{UF}} + Q_d) \times S_d$$

- Phénomène d'adsorption

Selon les propriétés physico-chimiques de certains antibiotiques, une certaine quantité d'antibiotique peut non pas être épurée par l'hémofiltre mais adsorbé. Ce phénomène d'adsorption est rapidement saturable et joue probablement un rôle négligeable dans la clairance totale de l'antibiotique. Ce phénomène semble affecter principalement les aminosides avec des membranes en polyacrylonitrile.<sup>70</sup>

Afin de tenir compte de ce phénomène dans la clairance induite par l'EER, le calcul de la clairance se fait à partir des concentrations d'antibiotiques mesurées en pré et post filtre selon les formules suivantes<sup>71</sup> :

$$Cl_{\text{EER}} = \frac{[\text{antibiotique}]_{\text{préfiltre}} - [\text{antibiotique}]_{\text{postfiltre}}}{[\text{antibiotique}]_{\text{préfiltre}}} \times Q_s$$

Une notion importante est celle de clairance extra-corporelle fractionnelle =  $CI_{EER}/CI$  totale. Il est communément admis qu'une clairance régionale contribuant à >25% de la clairance totale d'une molécule est cliniquement significative.

La clairance totale d'un antibiotique est la somme de toutes les clairances. Lorsqu'une EER est débutée, la clairance totale est égale à la somme de la CI rénale résiduelle + CI non rénale + CI EER.

### ***b) Analyse pharmacocinétique de population***

La deuxième approche plus complexe est l'analyse PK de population associant modélisation et simulations de Monte Carlo. Cette approche a fait l'objet de recommandations récentes de l'EMA et bénéficie désormais d'une reconnaissance réglementaire dans les phases de développement du médicament comme une alternative fiable aux études cliniques coûteuses de recherche de doses.<sup>72</sup>

#### Différences entre l'analyse PK classique et l'analyse PK de population

L'analyse PK de population a pour but de prédire les concentrations d'antibiotiques en fonction des caractéristiques des patients de la population d'intérêt. Elle diffère de l'analyse PK classique en deux points :

- elle repose sur une analyse mathématique plus complexe dite compartimentale pour décrire et prédire l'évolution des concentrations plasmatiques au cours du temps contrairement à l'analyse classique qui fait appel à une approche non-compartimentale, le plus souvent graphique (observations des  $C_{max}$ ,  $C_{min}$ , calcul de l'AUC par méthode trapézoïdale).

Un compartiment est défini comme un volume dans lequel toutes les molécules d'un médicament se comportent de la même manière et notamment diffusent avec la même

vitesse de transfert d'un compartiment à l'autre. Les entrées et sorties de chaque compartiment vont être décrits à l'aide d'équation différentielle.

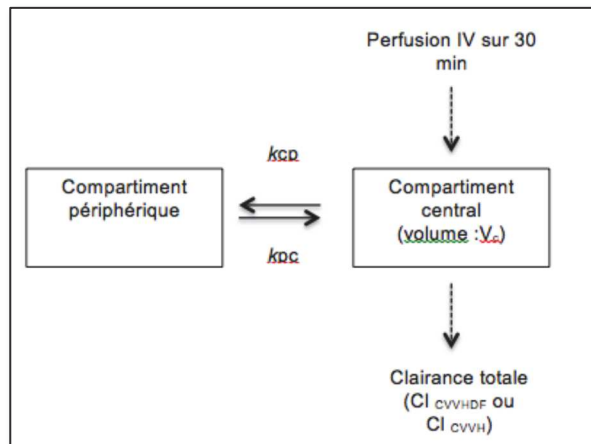


Figure 2. Exemple de modèle bicompartimental.

- elle repose sur une analyse de l'ensemble des données PK à l'échelon de la population et non plus de l'individu, bien que les prélèvements soient issus de différents individus.

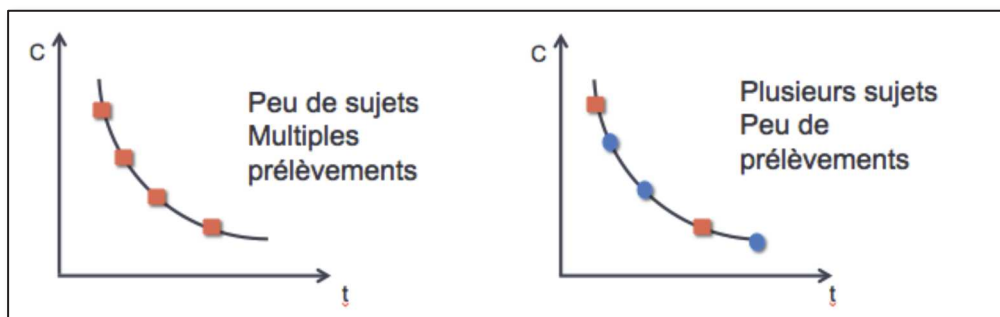


Figure 3. Schémas de prélèvements pour une analyse PK conventionnelle (à gauche), pour une analyse de population (à droite).

Un des avantages de cette approche réside dans la possibilité d'analyser des données éparses avec des temps de prélèvements différents rendant le plan expérimental moins contraignant. Cette étude de population permet de quantifier la variabilité du

comportement d'un médicament entre les individus, variabilité pouvant être à l'origine de la différence de réponse au traitement, et donc d'un risque d'échec ou de toxicité.

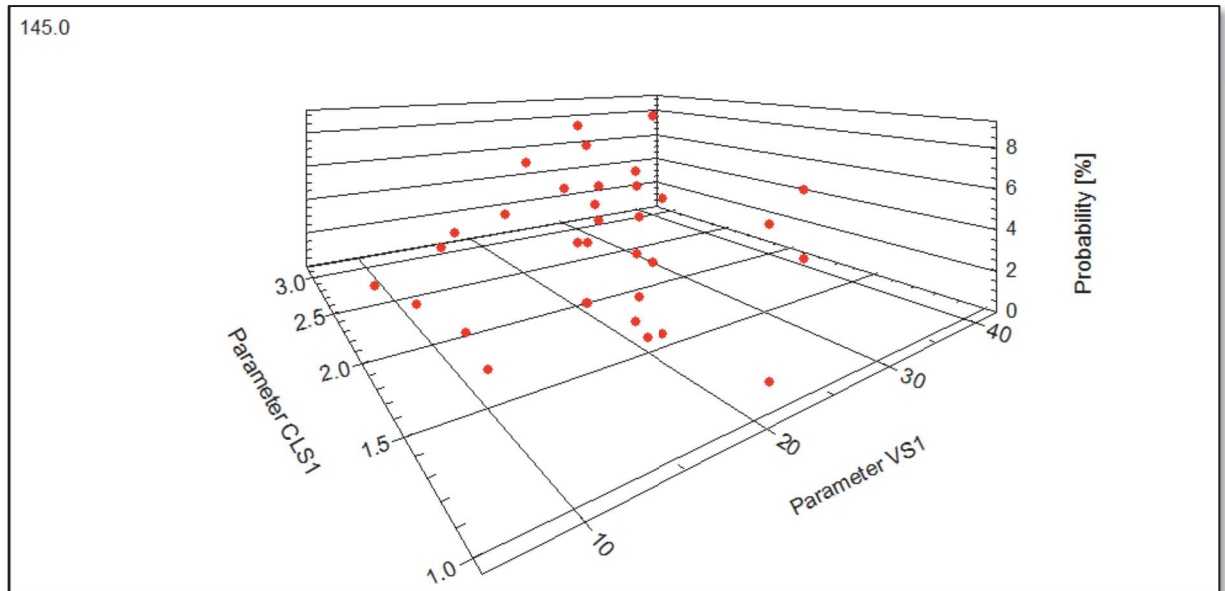
### Modélisation non linéaire à effets mixtes : quantifier la variabilité inter-individuelle

L'intérêt de la modélisation est de développer un modèle permettant de simuler l'évolution des concentrations pour différentes posologies ou schémas d'administration (bolus, perfusion continue avec ou sans dose de charge) non testés ou pour différentes valeurs de covariables affectant la PK (fonction rénale, poids, âge). Le modèle a pour but de décrire le comportement d'une molécule chez des patients aux caractéristiques différentes. Pour cela, les logiciels dédiés (NONMEM®, MONOLIX®, Pmetrics®) vont faire appel à une approche par modélisation non linéaire à effets mixtes. Les paramètres PK estimés vont être décrits par leur distribution reflétant la variabilité PK au sein de la population étudiée. Deux approches peuvent être distinguées : une approche dite paramétrique où l'hypothèse de la distribution des valeurs est faite *a priori* (distribution normale ou log-normale) et l'approche dite non paramétrique pour laquelle aucune hypothèse de distribution n'est définie *a priori*.<sup>73,74</sup>

Dans ce travail de thèse, l'approche non paramétrique à l'aide de l'algorithme non paramétrique NPAG (Non Parametric Adaptive Grid) du logiciel Pmetrics® a été choisie. Ce logiciel a été développé par le Laboratoire de Pharmacocinétique Appliquée (LAPK) de l'Université de Californie du Sud (USC).

Dans la première étape d'estimation des paramètres PK, le logiciel va déterminer un nombre fini de vecteurs de paramètres (ou jeux de paramètres) PK chacun associé à une probabilité. Le calcul du meilleur jeu de paramètres se fait par recherche du maximum de vraisemblance, par itérations successives, chaque itération améliorant la vraisemblance

(jusqu'à l'arrêt programmé de l'algorithme ou jusqu'à atteindre un critère de convergence lorsque la vraisemblance ne s'améliore plus entre deux itérations). Cet algorithme a déjà montré son intérêt dans plusieurs études pharmacocinétiques.<sup>75,76</sup>



Adapté de « Pmetrics User Manual »

Le modèle va comprendre des données connues (dose, temps d'administration) et des paramètres PK dit « effets fixes » et des paramètres qui vont varier au sein de la population étudiée dit « effets aléatoires ».

Variabilité inter-individuelle : rôle des covariables

Prenons l'exemple d'un antibiotique majoritairement éliminé par le rein. Le modèle peut relier la variabilité de la clairance de l'antibiotique à la clairance de la créatinine (ClCr) :  $Cl_{\text{population}} = a \times ClCr + b$ . Dans ce cas, les patients ayant une fonction rénale normale auront une clairance de l'antibiotique proche de la clairance moyenne. Les patients présentant une insuffisance rénale auront une clairance de l'antibiotique diminuée par

rapport à la clairance moyenne de la population. Le modèle pourra donc tenir compte de la variabilité inter et intra-individuelle des valeurs de la clairance de la créatinine pour expliquer tout ou partie de la variabilité des concentrations plasmatiques d'antibiotique observée. Ce modèle permet d'intégrer directement la relation entre un paramètre PK (Cl, Vd) et une ou des covariables (ClCr, fonction hépatique, poids, sexe, etc...) et donc de prédire les concentrations pour tout type de patient. Cette relation entre paramètre PK et covariable peut être linéaire ou non linéaire selon la variable considérée. Plusieurs covariables peuvent être introduites dans la même analyse selon une approche pas-à-pas (*forward insertion, backward deletion*). Toutefois, le principe de parcimonie est une règle fondamentale pour l'analyse pharmacocinétique qui privilégie le modèle le plus simple.

#### Variabilité résiduelle

La variabilité résiduelle est représentée par la variabilité intra-individuelle et la variabilité liée à l'erreur de mesure. La mesure des concentrations plasmatiques d'antibiotiques fait appel à des techniques d'HPLC +/- couplée à une spectrométrie de masse. Ces techniques de dosages sont associées à une sensibilité et une valeur de précision les plus basses possibles. Toutefois, les valeurs mesurées ne peuvent être considérées comme parfaitement exactes. Il peut également exister des différences liées à la calibration de la technique ou lorsque des séries de mesures sont faites à des moments distincts. Le modèle va donc également intégrer un modèle d'erreur qui sera appliqué à chaque concentration prédite pour pondérer chaque concentration de son incertitude liée à ces erreurs de mesure. Dans le cas du logiciel Pmetrics® utilisé dans ce travail de thèse, le modèle est un polynôme d'erreur de mesure, de degré variable dont la formule est la suivante :

$$SD = C_0 + C_1 XY + C_2 XY^2 + \dots$$

La valeur d'erreur appliquée diffère selon la concentration mesurée.



A ce modèle d'erreur s'ajoute un coefficient multiplicateur (gamma) ou additif (lambda) pour intégrer les autres sources d'erreur plus difficilement quantifiables tels que les erreurs dans les temps de prélèvements ou les doses administrées. La qualité des données recueillies va minimiser ce coefficient.

Variabilité inter-occasion

Cette variabilité correspond à des modifications potentielles de la PK de l'antibiotique au cours du temps, si des cinétiques sont réalisées à plusieurs jours voire plusieurs semaines ou mois d'intervalles.

### *c) Approche bayésienne*

L'approche utilisée dans ce travail de thèse est basée sur une approche dite bayésienne. Cette approche fait référence au théorème de Bayes et la probabilité a posteriori d'un événement A sachant a priori l'événement B :

$$P(A/B) = \frac{P(B/A) \cdot P(A)}{P(B/A)}$$

$P(A/B)$  : probabilité a posteriori de A sachant B

$P(A)$  : probabilité a priori de A (marginale de A)

$P(B)$  : probabilité a priori de B (marginale de B)

$P(B/A)$  : probabilité de B sachant A (fonction de vraisemblance de A)

Dans le cas de l'approche PK, il s'agit de la probabilité d'observer ces valeurs de paramètres PK dans la population totale sachant la valeur de la concentration C obtenue au temps t après l'administration d'une dose connue. Le but est de maximiser la vraisemblance de ces valeurs de paramètres PK telle que la concentration prédite par le modèle soit le plus proche possible de la concentration observée. Le critère bayésien est

représenté ici par l'association des paramètres PK de population et la concentration observée chez l'individu pour estimer a posteriori les paramètres PK individuels.

#### *d) Choix du modèle*

Le développement d'un modèle PK de population est un processus complexe et fastidieux. Il nécessite à chaque étape une inspection des graphes diagnostiques permettant de visualiser les concentrations observées et prédites et d'évaluer l'écart à la ligne de régression linéaire. Les capacités prédictives du modèle sont évaluées par le biais (moyenne des écarts entre concentrations prédites et observées) et la précision (moyenne des carrés des écarts entre concentrations prédites et observées), comme recommandé par Sheiner et collaborateurs.<sup>77</sup>

Dans le cas où deux modèles seraient jugés acceptables, ils sont alors comparés entre eux. Le critère de jugement retenu pour le choix du meilleur modèle est le critère d'Akaike (AIC).<sup>78</sup>

La formulation du critère d'Akaike est la suivante :

$$AIC = (2\hat{\sigma}^2 k) - 2\hat{\sigma}^2 \ln(L)$$

Avec : k : nombre de paramètres, L : vraisemblance.

Après comparaison des AIC des deux modèles, le candidat présentant la plus faible valeur d'AIC sera retenu.

Lors d'une deuxième étape de sélection, la comparaison des modèles est effectuée à l'aide d'un algorithme de recherche des  $k$  plus proches voisins.

#### *e) Simulations de Monte Carlo et probabilité d'atteindre la cible*

Le modèle PK développé va permettre de décrire la variabilité observée dans la population et de prendre en compte les covariables affectant la PK de l'antibiotique analysé.

A partir de ce modèle, les vecteurs de paramètres PK associés à leur probabilité vont être utilisés comme valeurs a priori pour tester différents schémas posologiques dans une population virtuelle de patients (classiquement entre 1000 et 5000). L'évolution des concentrations au cours du temps vont être prédites à partir de cette distribution des vecteurs de paramètres PK. Après avoir défini la cible PK/PD à atteindre (par exemple,  $AUC_{0-24}/CMI = 80$  pour le linézolide), le logiciel va compiler l'ensemble des  $AUC_{0-24}$  prédites dans cette population virtuelle et va calculer la probabilité d'atteindre la cible d' $AUC_{0-24}/CMI$  pour différentes valeurs de CMI afin de prendre en considération la sensibilité des germes.

Ces simulations dites de Monte Carlo présentent l'avantage de permettre la comparaison de différentes stratégies thérapeutiques virtuelles, sans contraintes réglementaires, éthiques ou économiques.

## ***6. APPLICATION DE LA MODELISATION PK/PD A 5 CLASSES D'ANTIBIOTIQUES FREQUEMMENT ADMINISTRES AU COURS DU SEPSIS***

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Dans cette partie de la thèse, nous avons tâché d'élaborer des modèles PK/PD pour plusieurs classes d'antibiotiques fréquemment utilisés dans le sepsis et pouvant, du fait de leurs propriétés physico-chimiques distinctes, être impactés de façon différente par l'EER et le sepsis. Ces modèles ont été développés à l'aide de l'algorithme non paramétrique NPAG du logiciel Pmetrics® dans l'interface R. Ces modèles nous ont ensuite permis de tester, à l'aide de MCS, différentes stratégies thérapeutiques afin de déterminer le mode d'administration et les posologies optimales de ces molécules.

Nous nous sommes dans un premier temps intéressés à la classe d'antibiotiques « à risque » que sont les aminosides, du fait de leur index thérapeutique étroit, leur caractère hydrophile et leur élimination quasi exclusivement rénale.

**Article 3 : Analyse PK de population de l'amikacine dans une population de patients septiques sous CVVH vs CVVHDF. *AAC, rang B, impact factor 2016 : 5,07.*<sup>79</sup>**

Comme nous l'avons vu dans l'article 1 et 2, le sepsis va altérer le comportement des aminosides et augmenter le risque de sous-dosage plasmatique.<sup>41,44</sup> Leur élimination majoritairement rénale les rend particulièrement vulnérables aux modifications de fonction rénale. Lorsqu'une EERc est appliquée une partie de l'aminoside va être épuré par l'hémofiltre. Il est communément admis que la clairance induite par la CVVHD est supérieure à la clairance induite par la CVVHDF elle même supérieure à la clairance induite par la CVVH.<sup>62,80</sup> Des études antérieures ont rapporté des clairances extra-corporelles fractionnelles très variables selon la technique utilisée.<sup>81-83</sup> L'intérêt de ce travail était de comparer l'impact de deux techniques différentes d'EERc sur la PK de l'amikacine : la CVVH et la CVVHDF appliquées à doses « équivalentes » de 30 mL/kg/h. Pour cela, 20 profils PK issus de 16 patients en choc septique et sous EERc ont été analysés. Une approche par analyse PK de population a été choisie. Plusieurs modèles structurels ont été testés, le modèle bi-compartmental étant celui décrivant le mieux les données PK. L'approche pour évaluer l'influence du type d'EER a consisté à modéliser la clairance de l'amikacine selon la technique utilisée, CVVH ou CVVHDF. L'analyse des covariables par l'approche pas-à-pas n'a retenu, dans le modèle final, comme seule covariable corrélée à la clairance totale de l'amikacine, le poids réel. L'introduction de cette covariable dans le modèle a entraîné une diminution du critère d'Akaike (AIC) de 801 à 786 et améliorer le « fit » du modèle.

La clairance totale de l'amikacine estimée pour le groupe des patients sous CVVH était de  $4,45 \pm 2,35$  L/h et  $4,69 \pm 2,42$  L/h pour le groupe de patients sous CVVHDF. Le Vd de l'amikacine était de  $25,2 \pm 17,3$  L soit un Vd de  $0,31 \pm 0,21$  L/kg. L'analyse mécanistique réalisée à partir des concentrations pré et post filtre retrouvait une clairance liée à l'EERc de  $1,8 \pm 1,3$  L/h pour le groupe CVVHDF versus  $1,3 \pm 1,0$  L/h pour le groupe CVVH,  $p=0,21$ . Bien que la différence ne soit pas statistiquement significative, on observe une clairance supérieure pour la technique d'EERc comprenant un principe diffusif.

Le modèle PK développé a été par la suite utilisé pour simuler différentes stratégies d'intervalles de dose (toutes les 24, 36 ou 48 h) et schémas posologiques (15 à 35 mg/kg) d'amikacine pour les deux techniques d'EERc. Les  $C_{\max}$  simulés ont été confrontés à des valeurs de CMI allant de  $\leq 1$  à 8 mg/L avec une cible atteinte lorsque le ratio  $C_{\max}/CMI$  était supérieur ou égal à 8.<sup>32</sup> Concomitamment, les  $C_{\min}$  simulées étaient confrontées aux valeur seuil de toxicité (2,5 mg/L pour l'amikacine et 0,5 mg/L pour la gentamicine). La probabilité d'atteindre cette cible double a été calculée pour chaque scénario posologique. Le schéma d'administration de fortes doses d'amikacine et d'espacement des intervalles de doses à minimum 36 voire 48h était dans cette étude le mode d'administration le plus optimal quelque soit la technique d'EER considérée pour optimiser l'efficacité thérapeutique et minimiser la toxicité. Dans la dernière étape de cette analyse PK de population, les probabilités d'atteindre la cible étaient confrontées à la fréquence de distribution des CMI de plusieurs entérobactéries obtenues à partir de la base de données de l'EUCAST. Pour les pathogènes difficiles à traiter tels que *Pseudomonas aeruginosa* et *Acinetobacter baumannii*, des posologies très élevées (35 mg/kg) sont requises pour atteindre les concentrations cibles selon les résultats des MCS. Certains auteurs ont suggéré l'utilisation de très fortes posologies d'amikacine (jusqu'à 50 mg/kg) et la mise en

place d'une EERc juste après la perfusion d'aminosides afin d'en limiter la toxicité rénale.<sup>84,85</sup>

**Conclusion : Ce travail propose, pour la population de patients en choc septique sous EERc, un schéma posologique de l'amikacine permettant de maximiser l'efficacité thérapeutique tout en minimisant le risque de toxicité. L'utilisation de fortes posologies d'amikacine (25 mg/kg) est préconisée en raison d'un Vd augmenté ; L'espacement des intervalles de doses permet d'obtenir une concentration résiduelle dans la cible recommandée (2,5 mg/L pour les recommandations françaises<sup>22</sup>).**

Article 3. Analyse PK de population de l'amikacine dans une population de patients septiques sous CVVH vs CVVHDF. AAC, rang B, impact factor 2016 : 5,07.<sup>79</sup>



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## Influence of Renal Replacement Modalities on Amikacin Population Pharmacokinetics in Critically Ill Patients on Continuous Renal Replacement Therapy

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The objective of this study was to describe amikacin pharmacokinetics (PK) in critically ill patients receiving equal doses (30 ml/kg of body weight/h) of continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF). Patients receiving amikacin and undergoing CVVH or CVVHDF were eligible. Population pharmacokinetic analysis and Monte Carlo simulation were undertaken using the Pmetrics software package for R. Sixteen patients (9 undergoing CVVH, 11 undergoing CVVHDF) and 20 sampling intervals were analyzed. A two-compartment linear model best described the data. Patient weight was the only covariate that was associated with drug clearance. The mean  $\pm$  standard deviation parameter estimates were 25.2  $\pm$  17.3 liters for the central volume, 0.89  $\pm$  1.17 h<sup>-1</sup> for the rate constant for the drug distribution from the central to the peripheral compartment, 2.38  $\pm$  6.60 h<sup>-1</sup> for the rate constant for the drug distribution from the peripheral to the central compartment, 4.45  $\pm$  2.35 liters/h for hemodiafiltration clearance, and 4.69  $\pm$  2.42 liters/h for hemofiltration clearance. Dosing simulations for amikacin supported the use of high dosing regimens ( $\geq$ 25 mg/kg) and extended intervals (36 to 48 h) for most patients when considering PK/pharmacodynamic (PD) targets of a maximum concentration in plasma ( $C_{max}$ )/MIC ratio of  $\geq$ 8 and a minimal concentration of  $\leq$ 2.5 mg/liter at the end of the dosing interval. The mean clearance of amikacin was 1.8  $\pm$  1.3 liters/h by CVVHDF and 1.3  $\pm$  1 liters/h by CVVH. On the basis of simulations, a strategy of an extended-interval high loading dose of amikacin (25 mg/kg every 48 h) associated with therapeutic drug monitoring (TDM) should be the preferred approach for aminoglycoside treatment in critically ill patients receiving continuous renal replacement therapy (CRRT). (This study is a substudy of a trial registered at ClinicalTrials.gov under number NCT01403220.)

Aminoglycosides have been used for many years mostly in combination with other antibiotics to treat infections in critically ill patients. The optimal dosing regimen should achieve a pharmacodynamic (PD) target of a maximum concentration in plasma ( $C_{max}$ )/MIC ratio of  $\geq$ 8 to 10 and an area under the concentration-time curve (AUC) from time zero to 24 h ( $AUC_{0-24}$ ) of  $>$ 70 to 90 and should have the least toxicity possible, depending on the  $AUC_{0-24}$  and trough (minimum) concentrations ( $C_{min}$ s) (1–5). In critically ill patients undergoing renal replacement therapy (RRT), optimization of the antibiotic dosing regimen is a crucial but difficult issue. Critically ill patients have severely altered pharmacokinetics (PK) (increased volume of distribution or altered drug clearance) due to hypoalbuminemia, increased capillary permeability, or organ dysfunctions (6, 7). In patients with acute kidney injury (AKI), the extracorporeal clearance of drugs during RRT could significantly change antibiotic pharmacokinetics due to the type of RRT mode, hemofilter, fluid replacement mode (pre- or postdilution), or RRT settings applied. The physicochemical properties of the drug also influence the amount of drug cleared by continuous renal replacement therapy (CRRT). As amikacin is a small hydrophilic molecule with a very low level of protein binding, it is likely that CRRT affects amikacin PK. Instead of intermittent hemodialysis, CRRT techniques are widely used in critically ill patients, as better hemodynamic stability and lower metabolic changes associated with possible better long-term outcomes have been reported (8, 9). These

alterations could dramatically reduce the likelihood of achieving therapeutic exposures of these drugs.

In previous studies with intensive care unit (ICU) patients undergoing CRRT, amikacin clearance varied from 0.53 to 5.34 liters/h, accounting for 40 to 89% of the total body clearance (10–15). These studies also reported conflicting results on the correlation between drug clearance and CRRT settings (11, 14). As a general rule, it is expected that the efficiency of drug removal would be higher in continuous venovenous hemodiafiltration (CVVHDF; diffusive and convective technique) modalities than in continuous venovenous hemofiltration (CVVH; convective technique) modalities (16). However, the pharmacokinetics of amikacin between these two different CRRT modalities using equal weight-based doses (effluent rate = 30 ml/kg of body weight/h, regardless of the technique used) have never been com-

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TABLE 1 Descriptive data for the studied population<sup>a</sup>

Demographic data	Result
No. of females/no. of males	4/12
Median (IQR) age (yr)	72 (65–75)
Median (IQR) wt (kg) at admission	80 (73–89)
Median (IQR) ht (cm)	167 (162–178)
Median (IQR) body mass index (kg/m <sup>2</sup> )	27 (24–32)
No. of patients with the following comorbidity:	
Hypertension	8
Chronic heart failure	2
COPD	2
Cirrhosis	1
Nondialysis chronic renal disease	2
Median (IQR) severity score	
SAPS II at admission	51 (41–59)
SOFA score at admission	10 (8–12)

<sup>a</sup> Data are for 16 patients. COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment.

pared. Indeed, a better understanding of the influence of different CRRT modalities on the PK/PD of aminoglycosides in critically ill patients may lead to optimized dosing strategies that could improve patient care.

The aim of the present study was to describe the pharmacokinetics of amikacin in ICU patients undergoing CVVH or CVVHDF with equal weight-based doses. Using population pharmacokinetic modeling and Monte Carlo simulations, we aimed to determine optimized amikacin dosing regimens for these patients.

## MATERIALS AND METHODS

**Setting.** This observational pharmacokinetic study was a substudy of a randomized trial comparing the efficacy of equal doses of CVVH (a 30-ml/kg/h ultrafiltrate flow rate) and CVVHDF (a 15-ml/kg/h dialysate flow rate plus a 15-ml/kg/h ultrafiltrate flow rate) in a 16-bed tertiary referral ICU in Nîmes University Hospital (ClinicalTrials.gov NCT01403220; completed but as yet unpublished). Ethics approval was obtained from the local ethics committee of Nîmes, France (Comité de Protection des Personnes Sud Méditerranée III, 5 February 2012). Written informed consent was obtained from either the patient or the patient's nominated substitute decision maker.

**Study population.** Patient eligibility for this study was (i) AKI necessitating either CVVH or CVVHDF according to the randomly allocated mode in the primary study and (ii) a clinical indication for amikacin use.

Patients were randomized to CVVH or CVVHDF (according to the primary study protocol) when the need for RRT was first identified. If the patient subsequently had at least an 8-h break from RRT, then the protocol of the primary study required that the patient then receive the alternative RRT mode. When the patient was on antibiotic therapy across both RRT modes, the patient was sampled on two different occasions encompassing both CVVH and CVVHDF.

Patients were excluded if they had a (i) requirement for RRT for cardiogenic pulmonary edema, metabolic acidosis (pH <7.15, HCO<sub>3</sub><sup>-</sup> concentration, <12 mmol/liter), or hyperkalemia (potassium concentration, >6.5 mmol/liter) or (ii) a history of allergy to amikacin or a contraindication to treatment with amikacin.

**Renal replacement therapy settings.** Both techniques were performed using an Aquarius system (Nikkiso, Japan) and a polysulfone-type hemofilter with a surface of 1.9 m<sup>2</sup> (Aquamax HF19).

The RRT settings were as follows. (i) A 30-ml/kg/h ultrafiltrate rate was used for CVVH and a 15-ml/kg/h ultrafiltrate rate plus a 15-ml/kg/h dialysate flow rate were used for CVVHDF. For both techniques, the replacement mode applied was the postdilution mode. (ii) The net fluid removal rate was set at the physician's discretion and was between 0 and 200 ml/h. (iii) The targeted blood flow rate was aimed at the provision of a filtration ratio of <20%. The filtration ratio was calculated as follows: filtration ratio = ultrafiltrate flow rate/blood flow rate. It is the fraction of plasma that is removed from blood during hemofiltration (17).

**Study protocol.** A dosing regimen of 15 to 30 mg/kg amikacin was administered intravenously (i.v.) over 30 min as part of the antimicrobial therapy prescribed for the patient. The subsequent doses were administered at doses and frequencies (typically every 24 or 36 h) according to the therapeutic drug monitoring results. Prefilter blood samples to determine plasma amikacin concentrations were taken at the baseline (predose), at the end of infusion (0.5 h), 30 min after the end of infusion (1 h), and 1.5, 2, 4, 8, 12, and 24 h after the start of infusion. Postfilter blood samples were taken up to 2, 4, 8, 12, and 24 h after the start of infusion.

**Sample handling, storage, and measurement.** Blood samples were immediately placed on ice and within 60 min were centrifuged at 3,000 rpm for 10 min and then stored at –80°C. Samples were transported by a commercial courier company to the Burns, Trauma, and Critical Care Research Centre, The University of Queensland, Brisbane, Queensland, Australia, for analysis. Amikacin concentrations ranging from 0.5 to 100 mg/liter in plasma were measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a hydrophilic interaction liquid chromatography (HILIC) column on a Shimadzu Nexera system coupled to a Shimadzu 8030+ triple-quadrupole mass spectrometer. Clinical samples were assayed alongside calibrators and quality controls and met the batch acceptance criteria of the U.S. Food and Drug Administration (U.S. FDA).

**Sample preparation.** Plasma (100 µl) was spiked with the internal standard (vancomycin), and 15% trichloroacetic acid was added to precipitate the proteins. An aliquot of 0.2 µl of the supernatant extract was injected onto the LC-MS/MS.

**Chromatography.** The stationary phase was an Agilent Poroshell 120 HILIC column (2.1 by 50 mm, 2.7 µm, 120 Å). The mobile phase used was a gradient with mobile phase A, consisting of 0.2% (vol/vol) formic acid, and mobile phase B, consisting of acetonitrile with 0.2% (vol/vol) formic acid. The flow rate was 0.3 ml/min.

**Validation.** The assay method was validated for linearity, lower limit of quantitation, matrix effects, precision, accuracy, stock solution stability, long-term storage stability, and freeze-thaw stability using the U.S. FDA criteria for bioanalysis. Precision and accuracy were within 8.9%, 2.8%, and 1.5% at the three concentrations tested (1.5, 14, and 60 mg/liter), respectively. The limit of detection was 0.07 mg/liter.

TABLE 2 Clinical data and RRT parameters during RRT sessions<sup>a</sup>

RRT	C <sub>max</sub> (mg/liter)	C <sub>min</sub> (mg/liter)	Dosing interval (h)	12-h urine output	MAP (mm Hg)	Heart rate (no. of beats/min)	Albumin concn (g/liter)	Creatinine concn (µmol/liter)
CVVHDF (n = 11)	52.9 (29.8–68.4)	3.1 (1.6–3.5)	24 (24–38)	110 (98–338)	77 (72–84)	92 (83–102)	27.6 (22–30.7)	243 (191–300)
CVVH (n = 9)	60.6 (44.5–86.7)	2.9 (2.5–3)	24.5 (24–34)	700 (30–725)	70 (67–86)	100 (70–106)	27.9 (22.8–29.8)	248 (211–280)

<sup>a</sup> Data are expressed as the median (IQR). CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; MAP, mean arterial pressure; RRT, renal replacement therapy; NA, not available.



**Patient data collection.** Additional clinical and demographic data were collected, including the simplified acute physiology score II (SAPS II) (18) at ICU admission, the modified sequential organ failure assessment (SOFA) (19) score, comorbidities, and 28-day outcome. During the RRT treatment, CVVH or CVVHDF settings were also recorded. The type of infection, the antimicrobial agents administered, microbiological culture results, and Etest MICs (bioMérieux, Marcy l'Etoile, France) (if available) were collected.

**Population pharmacokinetic modeling.** One- and two-compartment models were developed with the nonparametric adaptive grid (NPAG) algorithm within the freely available Pmetrics software package for R (Laboratory of Applied Pharmacokinetics, University of Southern California, Los Angeles, CA) (20, 21). Elimination from the central compartment and the intercompartmental distribution (two-compartment model) into the peripheral compartment were modeled as first-order processes.

**Population pharmacokinetic covariate screening.** Actual body weight, serum creatinine concentration, serum albumin concentration, age, SOFA score, vasopressor use, residual renal function, filter age, and the difference in the patient's weight between the time of admission and the sampling day were evaluated as covariates. If inclusion of the covariate resulted in a statistically significant improvement in the log-likelihood values ( $P < 0.05$ ) and/or improved the goodness-of-fit plots, then it was included.

**Model diagnostics.** Goodness of fit was assessed by linear regression with an observed-predicted plot, coefficients of determination, and log-likelihood values. Predictive performance evaluation was based on the mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) for the population and individual prediction models. Using the final covariate model, a visual predictive check (VPC) was performed using the bootstrapping method by simulating 1,000 subjects to assess the predictive performance of the model.

**PTA.** Monte Carlo simulations ( $n = 1,000$ ) were employed using Pmetrics to determine the probability of target attainment (PTA) for the PK/PD targets, which were a  $C_{max}/MIC$  ratio of  $\geq 8$  (2, 3, 5) or an AUC/MIC of  $\geq 70$  (3, 5), for various MICs (0.125 to 32 mg/liter) during the first 24 h of treatment for patients with total body weights of 60 kg, 80 kg, and 100 kg. Supratherapeutic exposures were described as a trough concentration ( $C_{min}$ ) of  $\geq 2.5$  mg/liter, in line with French national guidelines (22).

**Fractional target attainment calculation.** MIC data for *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* from the EUCAST database (available at [www.eucast.org](http://www.eucast.org); accessed 30 December 2015) were used to determine fractional target attainment. The fractional target attainment identifies the likely success of treatment by comparing the pharmacodynamic exposure (PTA) against an MIC distribution. A priori, a dosing regimen was considered successful if the fractional target attainment was  $\geq 85\%$  (34).

**Estimation of the clearance of amikacin by CRRT.** The clearance of amikacin by CRRT was assessed as follows: amikacin clearance by CCRT =  $(C_{pre} - C_{cor\_post})/C_{cor\_post} \cdot BFR$ , where  $C_{pre}$  is the amikacin prehemofilter concentration,  $C_{cor\_post}$  is the corrected amikacin posthemofilter concentration, and BFR is the blood flow rate. Posthemofilter concentrations were corrected for postdilution as follows:  $C_{cor\_post} = C_{post} \cdot (BFR - PDR - FRR)/BFR$ , where  $C_{post}$  is the measured amikacin posthemofilter concentration, BFR is the blood flow rate, PDR is the postdilution flow rate, and FRR is the fluid removal rate.

TABLE 2 (Continued)

Urea concn (mmol/liter)	Blood flow rate (ml/min)	Dialysate flow rate (ml/kg/h)	Ultrafiltration rate (ml/kg/h)	Fraction filtration ratio (%)	RRT downtime (h)	Filter age (h)	Transmembrane pressure (mm Hg)	Fluid removal rate (ml/kg/h)
20 (12–25)	200 (180–215)	15.4 (15.1–16.4)	16.3 (14–16.9)	11 (9–12)	0.15 (0–1)	15 (4–21)	39 (20–52)	17 (15–17)
12 (8.2–15.4)	250 (200–250)	NA	33.3 (31.2–36.8)	20 (18–21)	0.15 (0–0.75)	15 (14–21)	77 (72–86)	21 (17–21)

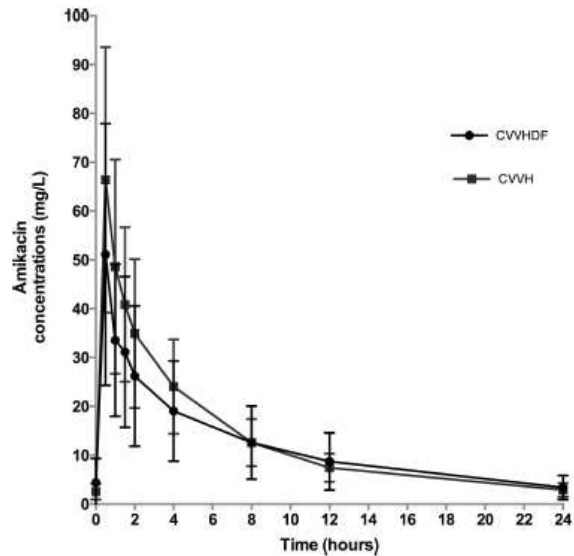


FIG 1 Observed mean concentration-time profiles for the amikacin dosing sampling interval in critically ill patients receiving CVVH ( $n = 9$ ) or CVVHDF ( $n = 11$ ). Error bars represent standard deviations.

**Statistical analysis.** Continuous data are presented as the mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR). Categorical data are presented as counts (in percent). Comparisons used the Mann-Whitney U and chi-square tests as appropriate. Correlations were assessed by means of a scatter graph and the Pearson correlation coefficient ( $r$ ). Differences in amikacin clearance by CVVH and CVVHDF were analyzed using a Student  $t$  test. A  $P$  value of  $<0.05$  was considered statistically significant, and all analyses were performed using GraphPad Prism software (version 6.0; San Diego, CA, USA).

## RESULTS

**Demographic and clinical data.** Sixteen patients were recruited into the study per the study protocol, and data from 20 RRT sessions were analyzed. Demographic data are presented in Table 1. The patients included in the study required vasopressor support during 17 (85%) RRT sessions. The patients had pulmonary ( $n = 4$ ), intra-abdominal ( $n = 7$ ), urinary tract ( $n = 4$ ), and vascular prosthesis ( $n = 1$ ) infections. The samples studied microbiologically were positive for 7 (44%) patients. One *Serratia marcescens* isolate, one multidrug-resistant (MDR) *K. pneumoniae* isolate, three *E. coli* isolates, one *Enterococcus faecium* isolate, one *Enterococcus faecalis* isolate, one *Morganella morganii* isolate, one MDR *Citrobacter braakii* isolate, three staphylococci (including one methicillin-resistant *Staphylococcus aureus* isolate and one MDR *Staphylococcus capitis* isolate), and two

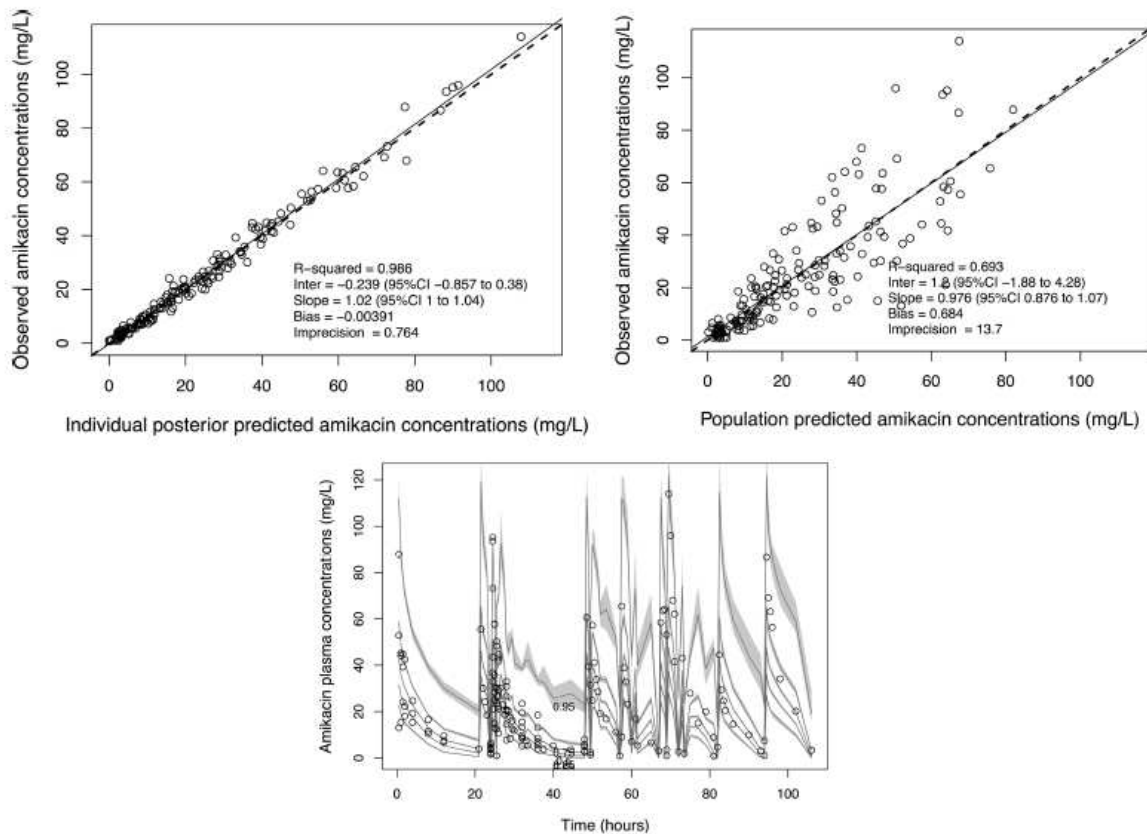


FIG 2 Diagnostic plots for the final covariate model. Observed versus population predicted concentrations (top right) and individual predicted concentrations (top left) in plasma. (Bottom) Visual predictive check. CI, confidence interval. Inter, intercept.

streptococci were identified. The MICs for the Gram-negative bacilli ranged from 2 mg/liter to 16 mg/liter. The MICs for the Gram-positive cocci ranged from 4 to 64 mg/liter. Among the 16 patients included, the 28-day mortality rate was 38%. Four of the six deaths were related to the infectious episode for which amikacin was prescribed.

**Replacement renal therapy.** Four patients underwent both CVVH and CVVHDF. Of the remaining patients, 5 received CVVH only and 7 received CVVHDF only. The RRT settings across both CVVH and CVVHDF treatments are shown in Table 2.

**Pharmacokinetic model building.** The mean observed concentration-time profile of amikacin is shown in Fig. 1. The blood samples were taken at a median time of 31 h (IQR, 16 to 69 h) after the start of amikacin therapy. A two-compartment linear model best described the time course of 261 total plasma concentrations of amikacin. This model included a zero-order input of drug into the central compartment. The only covariate that improved the fit of the model was, for amikacin clearance, weight normalized to 80 kg for CVVH and to 75 kg for CVVHDF (to the power of 0.75). After the inclusion of weight in the model, the  $-2$  log-likelihood value was reduced from 801 to 786, although the log-likelihood values were not statistically significantly

different ( $P = 0.55$ ), and the goodness of fit improved. For these reasons, weight was retained in the final model.

The final model was described as follows: amikacin  $CL = CL_{hr} \cdot [(WT/80)^{0.75}] + CL_{hdf} \cdot [(WT/75)^{0.75}]$ , where  $CL$  is clearance,  $WT$  is total body weight,  $CL_{hr}$  is total amikacin clearance on hemofiltration, and  $CL_{hdf}$  is total amikacin clearance on hemodiafiltration.  $CL_{hdf}$  was 0 when hemodiafiltration was applied, and  $CL_{hr}$  was 0 when hemofiltration was applied.

The mean population pharmacokinetic parameter estimates from the final covariate model were  $25.2 \pm 17.3$  liters for central volume,  $0.89 \pm 1.17$  liters/h for the rate constant for the drug distribution from the central to the peripheral compartment ( $k_{cp}$ ),  $2.38 \pm 6.60$  liters/h for the rate constant for the drug distribution from the peripheral to the central compartment ( $k_{pc}$ ),  $4.45 \pm 2.35$  liters/h for population mean total amikacin clearance on hemodiafiltration, and  $4.69 \pm 2.42$  liters/h for population mean total amikacin clearance on hemofiltration. The mean individual empirical Bayesian clearance estimates of the patients undergoing CVVH and CVVHDF were estimated to be  $5.19 \pm 0.74$  and  $4.08 \pm 0.50$  liters/h ( $P = 0.21$ ), respectively. The diagnostic plots to confirm the goodness of fit of the model were considered acceptable and are shown in Fig. 2. The final covariate model was then used for dosing simulations.

TABLE 3 Monte Carlo simulations and PTA in plasma for various i.v. amikacin doses for patients with body weights of 60 kg, 80 kg, and 100 kg undergoing CVVH or CVVHDF for various MICs<sup>a</sup>

RRT, body wt, and dosage	Achievement of the indicated PK/PD target for MIC of:							
	≤1 mg/liter		2 mg/liter		4 mg/liter		8 mg/liter	
	$C_{max}/MIC$ ratio ≥ 8	AUC/MIC ≥ 70	$C_{max}/MIC$ ratio ≥ 8	AUC/MIC ≥ 70	$C_{max}/MIC$ ratio ≥ 8	AUC/MIC ≥ 70	$C_{max}/MIC$ ratio ≥ 8	AUC/MIC ≥ 70
<b>CVVH</b>								
60 kg								
15q24	+	+	-	-	-	-	-	-
20q24	+	+	+	+	-	-	-	-
25q24	+	+	+	+	-	-	-	-
30q24	+	+	+	+	+	+	-	-
35q24	+	+	+	+	+	+	-	-
80 kg								
15q24	+	+	-	-	-	-	-	-
20q24	+	+	+	+	-	-	-	-
25q24	+	+	+	+	+	-	-	-
30q24	+	+	+	+	+	+	-	-
35q24	+	+	+	+	+	+	-	-
100 kg								
15q24	+	+	-	-	-	-	-	-
20q24	+	+	+	+	+	-	-	-
25q24	+	+	+	+	+	+	-	-
30q24	+	+	+	+	+	+	-	-
35q24	+	+	+	+	+	+	+	-
<b>CVVHDF</b>								
60 kg								
15q24	+	+	+	+	-	-	-	-
20q24	+	+	+	+	-	-	-	-
25q24	+	+	+	+	-	-	-	-
30q24	+	+	+	+	+	-	-	-
35q24	+	+	+	+	+	+	-	-
80 kg								
15q24	+	+	+	+	-	-	-	-
20q24	+	+	+	+	-	-	-	-
25q24	+	+	+	+	+	-	-	-
30q24	+	+	+	+	+	+	-	-
35q24	+	+	+	+	+	+	-	-
100 kg								
15q24	+	+	+	+	-	-	-	-
20q24	+	+	+	+	+	-	-	-
25q24	+	+	+	+	+	+	-	-
30q24	+	+	+	+	+	+	-	-
35q24	+	+	+	+	+	+	-	-

<sup>a</sup> The target was a  $C_{max}/MIC$  ratio of ≥8 and AUC/MIC of ≥70. CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; +, achievement of PK/PD target; -, nonachievement of PK/PD target; 15q24, 20q24, 25q24, 30q24, and 35q24, doses of 15, 20, 25, 30, and 35 mg/kg administered every 24 h, respectively.

**Dosing simulations.** The Monte Carlo simulations and PTAs of a  $C_{max}/MIC$  ratio of ≥8 and an AUC/MIC of ≥70 for various amikacin doses for patients that weighed 60 kg, 80 kg, or 100 kg are described in Table 3. The Monte Carlo simulations and PTAs of a  $C_{max}/MIC$  ratio of ≥8 and a  $C_{min}$  of ≥2.5 mg/liter for various amikacin dosing regimens for a patient that weighed 80 kg and for an isolate for which the MIC was 4 mg/liter are shown in Fig. 3 (CVVH) and Fig. 4 (CVVHDF). An MIC of 4 mg/liter was chosen to indicate that suboptimal achievement of therapeutic targets occurs at this MIC.

**Fractional target attainment.** The fractional target attainments for the simulated PTAs for a range of amikacin doses, dose intervals, and patient body weights against susceptible MIC distri-

butions (MICs ≤ 8.0 mg/liter) for *A. baumannii*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa* are shown in Table 4.

**Amikacin clearance across the hemofilter during CRRT.** The mean clearance of amikacin by CRRT was  $1.8 \pm 1.3$  liters/h by CVVHDF and  $1.3 \pm 1.0$  liters/h by CVVH.

## DISCUSSION

In the present study, the extended-interval high amikacin dose of 25 mg/kg every 48 h is optimal in critically ill patients undergoing CVVH or CVVHDF to achieve the PK/PD targets and to limit toxicity when infections with difficult-to-treat pathogens are suspected. Indeed, this dose and dosing interval led to the optimal amikacin exposure, as this dosing regimen provides the largest

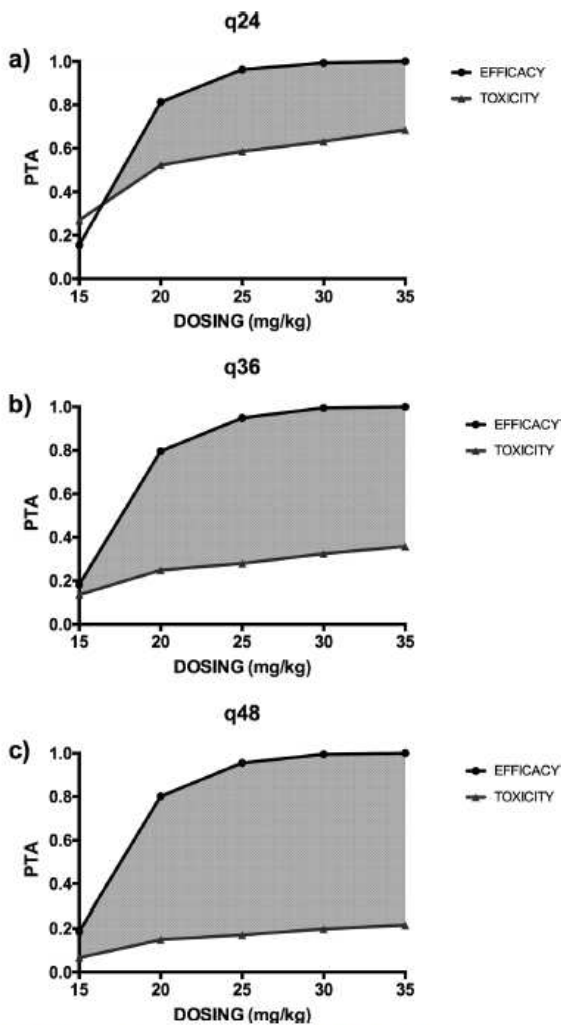


FIG 3 PTA of efficacy ( $C_{max}/MIC$  ratio  $\geq 8$ ) and toxicity ( $C_{min} \geq 2.5$  mg/liter at the end of the dosing interval) for a patient undergoing CVVH with a body weight of 80 kg with dosing every 24 h (q24) (a), 36 h (q36) (b), and 48 h (q48) (c) and targeting pathogens with an MIC of 4 mg/liter.

difference between the efficacy and the toxicity probability (23). Several studies have reported that the pharmacokinetics of aminoglycosides are altered in critically ill patients, leading to a  $C_{max}$  lower than the targeted  $C_{max}$  in 30 to 40% of critically ill patients using standard dosing regimens (24–27). The increased volume of distribution observed in critically ill patients and the concentration-dependent killing activity of aminoglycosides support the use of regimens with higher doses of amikacin to achieve adequate  $C_{max}$ s. The use of dosing regimens of  $\geq 25$  mg/kg in critically ill patients has been suggested by several authors and recommended by some national guidelines (13, 24, 27, 28). However, some concerns remain about aminoglycoside-related nephrotoxicity using high aminoglycoside dosing regimens, especially in patients with

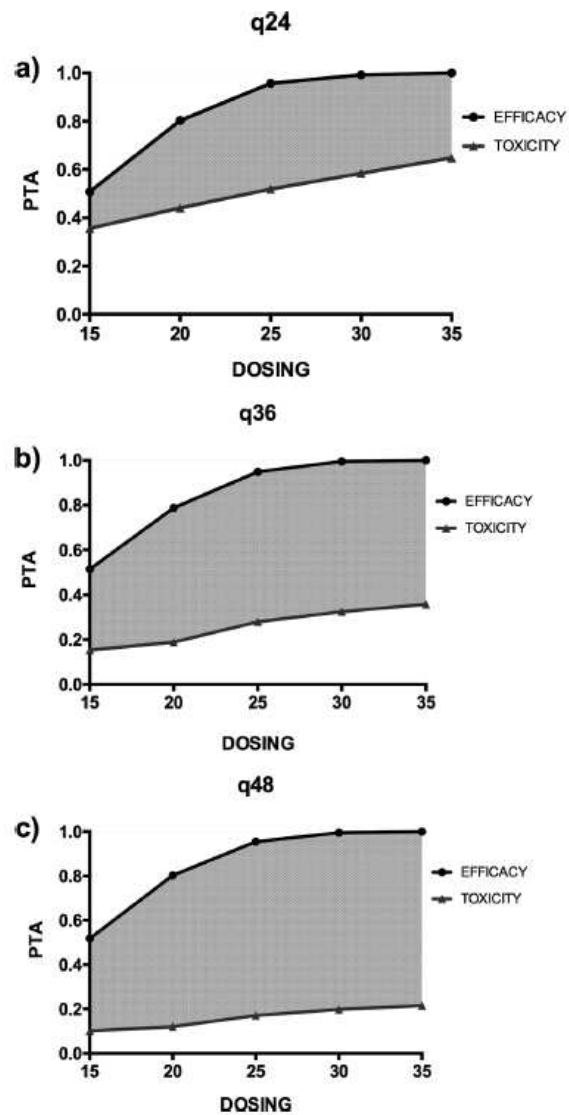


FIG 4 PTA of efficacy ( $C_{max}/MIC$  ratio  $\geq 8$ ) and toxicity ( $C_{min} \geq 2.5$  mg/liter at the end of the dosing interval) for a patient undergoing CVVHDF with a body weight of 80 kg with dosing every 24 h (a), 36 h (b), and 48 h (c) and targeting pathogens with an MIC of 4 mg/liter. Units for dosing are milligrams per kilogram.

AKI requiring RRT. Our results showed that the PK/PD targets ( $C_{max}/MIC$  ratio  $\geq 8$ ,  $AUC/MIC \geq 70$ ) were achieved with a dosing regimen of 25 mg/kg or higher in critically ill patients undergoing CVVH or CVVHDF. These results are consistent with those reported by Taccone et al. (11). They reported that a 25-mg/kg loading dose of amikacin in patients undergoing CVVHDF at a dose of 30 ml/kg/h and a blood flow rate setting at 150 to 200 ml/min achieved the targeted  $C_{max}$  of 64 mg/liter in 9 (69%) pa-

**TABLE 4** Fractional target attainment for the various amikacin doses every 24 h for patients with body weights of 60 kg, 80 kg, or 100 kg receiving CVVH or CVVHDF for susceptible MIC distributions for *A. baumannii*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa*<sup>a</sup>

Body wt (kg)	i.v. dose (mg/kg) <sup>b</sup>	RRT	Fractional target attainment <sup>c</sup> (%)				
			<i>A. baumannii</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
60	900 (15)	CVVHDF	65	91	73	53	
		CVVH	53	83	60	40	
	1,200 (20)	CVVHDF	74	94	82	64	
		CVVH	74	94	82	64	
	1,500 (25)	CVVHDF	82	96	88	74	
		CVVH	82	96	88	75	
	1,800 (30)	CVVHDF	88	97	93	83	
		CVVH	88	95	89	83	
	2,100 (35)	CVVHDF	92	98	96	88	
		CVVH	92	98	96	88	
	80	1,200 (15)	CVVHDF	74	94	82	64
			CVVH	53	83	59	40
1,600 (20)		CVVHDF	84	96	90	77	
		CVVH	85	96	90	78	
2,000 (25)		CVVHDF	91	98	95	86	
		CVVH	91	98	95	86	
2,400 (30)		CVVHDF	94	98	97	91	
		CVVH	94	98	97	91	
2,800 (35)		CVVHDF	96	99	98	94	
		CVVH	96	99	98	94	
100		1,500 (15)	CVVHDF	82	96	88	74
			CVVH	53	82	59	40
	2,000 (20)	CVVHDF	84	96	90	77	
		CVVH	91	98	95	86	
	2,500 (25)	CVVHDF	91	98	95	86	
		CVVH	94	98	97	91	
	3,000 (30)	CVVHDF	94	98	97	91	
		CVVH	97	99	98	95	
	3,500 (35)	CVVHDF	96	99	98	94	
		CVVH	98	100	99	98	

<sup>a</sup> CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration.

<sup>b</sup> Weight-based dosing regimens (in milligrams per kilogram) are given in parentheses.

<sup>c</sup> Gray shading, achievement of the a priori PTA of a  $C_{max}/MIC$  ratio of  $\geq 8$  against at least 85% of isolates.

tients. The amikacin clearance reported in that study widely varied between 0.006 and 0.198 liter/kg/h, but the mean clearance of amikacin was lower than that reported in the present study (11). The authors did not find any correlation between RRT settings and amikacin clearance. However, some RRT parameters, such as pre- or postdilution mode or downtime, were not recorded. RRT filter downtime is also a factor that may influence RRT-related drug clearance but is rarely reported. In the present study, the filter downtime was very low during the dosing interval and likely did not affect amikacin clearance, and only the postdilution mode was used.

As CVVHDF combines convection and diffusion processes to clear molecules from blood, there is a general assumption that clearance by CVVHDF is higher than clearance by CVVH (16). In the present study, using the recommended 30-ml/kg/h effluent rate for both modes (a 30-ml/kg/h ultrafiltrate flow rate for CVVH and a 15-ml/kg/h dialysate flow rate associated with a 15-ml/kg/h ultrafiltrate flow rate for CVVHDF) (29), similar blood flow rates, and similar membranes during the RRT sessions, we did not show any significant differences in amikacin clearance. It could be hypothesized that when the recommended high doses of the effluent

rate for continuous RRT are applied, the difference between convection and/or diffusion might not be significant for antibiotic pharmacokinetics (30).

Most importantly, none of the simulated dosing regimens achieved the PK/PD targets for the EUCAST MIC breakpoint of 8 mg/liter. These findings might encourage physicians to increase amikacin doses, but the increasing risk of renal toxicity should be considered. As the clearance decreases in the context of AKI, the drug half-life increases, in which case an extended dosing interval would be required to enable redosing at the recommended trough concentrations. In the present study, extended intervals (i.e., every 36 h up to every 48 h) achieved the lowest probability of toxicity without an apparent decrease in efficacy. Extending the dosing interval may allow a drug-free period and may reduce the risk of aminoglycoside accumulation in the renal cortex. In a previous study, we highlighted that the use of a regimen with a higher dose (30 mg/kg) in association with therapeutic drug monitoring led to extended dosing intervals in half of the critically ill patients studied (28). Taccone et al. reported that the median time to achieve a trough concentration below 5 mg/liter was 36 h (IQR, 14 to 76 h) in patients undergoing CVVHDF (11). The extended dosing in-

tervals suggested by the results of the present study are consistent with recommendations for aminoglycoside dosing regimens in critically ill patients receiving continuous RRT (30–32). However, as highlighted by the results of the present study, regimens with doses higher than those recommended (e.g., a loading dose of 10 mg/kg and maintenance doses of 7.5 mg/kg every 24 to 48 h) should be used to ensure efficacy and to limit toxicity at the same time. Some authors have even suggested that a dosing regimen of 50 mg/kg of amikacin followed by continuous RRT be used to limit toxicity in a patient with a multidrug-resistant *P. aeruginosa* infection (33).

The present study has limitations to consider. First, we could not assess mechanistically if the concentrations observed were caused by RRT or non-RRT clearance because the clearance of amikacin into the RRT effluent was not available in this study, although this limitation does not alter our dosing recommendations. Moreover, no correlation between residual renal function and amikacin clearance was found in this model. Second, we used a targeted trough concentration of 2.5 mg/liter to define aminoglycoside-related renal toxicity, even though its relevance could be questioned. However, French guidelines recommend redosing only when aminoglycoside trough concentrations are below 2.5 mg/liter. Third, further prospective studies need to confirm that extended dosing intervals do not reduce the antimicrobial effects of aminoglycosides.

**Conclusion.** In the present study, we observed a high degree of variability in the pharmacokinetics of amikacin in critically ill patients. Suboptimal achievement of therapeutic targets for the EUCAST breakpoint of 8 mg/liter occurs when standard dosing is used. We recommend a loading dose of 25 mg/kg every 48 h adjusted according to the findings of therapeutic drug monitoring as the preferred approach for aminoglycoside treatment in critically ill patients receiving continuous renal replacement therapy.

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C.R. made substantial contributions to study conception, study design, acquisition and interpretation of the data, and drafting of the manuscript and approved the final version to be published. S.C.W. made substantial contributions to acquisition, analysis, and interpretation of the data, revised the manuscript for important intellectual content, and approved the final version to be published. L.M. made substantial contributions to study conception, study design, interpretation of the data, and drafting of the manuscript and approved the final version to be published. G.S. made substantial contributions to acquisition, analysis, and interpretation of the data, revised the manuscript for important intellectual content, and approved the final version to be published. J.L. made substantial contributions to study conception, study design, interpretation of the data, and drafting of the manuscript and approved the final version to be published. J.A.R. made substantial contributions to study conception, study design,

analysis and interpretation of the data, and drafting of the manuscript, revised the manuscript for important intellectual content, and approved the final version to be published.

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**Article 4 : Analyse PK de population du linézolide dans une population de patients septiques sous CVVH vs CVVHDF. *JAC, rang A, impact factor 2016 : 5,07.*<sup>86</sup>**

Nous avons, dans un second travail, appliqué la même méthodologie mais cette fois-ci en nous intéressant à un antibiotique lipophile avec une élimination rénale modérée et une activité bactéricide temps-dépendante et concentration-dépendante : le linézolide. Cet antibiotique est administré pour le traitement des infections à cocci Gram positifs multi-résistants. Pour cette classe d'antibiotique, l'AUC/CMI est l'indice PK/PD le mieux corrélé à l'efficacité thérapeutique.<sup>87</sup> Du fait de ses propriétés physico-chimiques, la PK du linézolide pourrait, en théorie, ne pas être fortement impactée par l'EERc. Cependant, peu de données sont disponibles pour cette population de patients et les résultats contradictoires quant à l'impact de la dialyse sur sa PK.<sup>88</sup> Dans une population de patients de réanimation, Meyer et al. Retrouvaient des paramètres PK comparable à ceux des volontaires sains.<sup>88</sup> D'autres études de faible effectif ont rapporté une clairance extra-corporelle fractionnelle du linézolide très variable allant de 12 à 33%.<sup>89</sup> Dans notre travail, nous avons comparé deux techniques d'EERc : la CVVH à la dose de 30 mL/kg/h et la CVVHDF à la dose de 15 mL/kg/h de filtration et 15 mL/kg/h de dialysat. Le linézolide était administré en perfusion d'1 heure à la posologie de 600 mg toutes les 12 heures. Afin de définir les schémas posologiques optimaux du linézolide dans la population de patients septiques sous EERc, nous avons développé un modèle PK/PD dans le logiciel Pmetrics® à partir de 9 profils PK sous CVVHDF et 8 profils sous CVVH. Des modèles à deux et trois compartiments ont été testés. Le modèle bi-compartimental comprenant le score SOFA et le poids comme covariables explicatives du Vd a été choisi comme modèle final après comparaison des AIC et des graphes diagnostiques. Nous avons également testé l'introduction dans le modèle de deux clairances différentes selon la technique d'EERc



utilisée sans amélioration du modèle. Seule la clairance totale pour l'ensemble de la population a été estimée dans le modèle final à  $3,8 \pm 2,2$  L/h et le volume central était estimé à  $26,5 \pm 10,3$  L. L'analyse des valeurs de paramètres PK individuelles dites « postérieures » rapportaient une clairance totale dans le groupe CVVHDF supérieure (5,9 L/h) comparée au groupe CVVH (4,5 L/h) bien que la différence ne soit pas significative ( $p=0.39$ ).

Les simulations de Monte Carlo ont permis d'identifier deux cas de figure où les posologies conventionnelles de linézolide semblent ne pas être adaptées :

- 1°) pour les patients avec un poids corporel réel supérieur à 90 kg
- 2°) pour traiter des bactéries présentant des CMI élevées ( $\geq 2$  mg/L)

L'optimisation des posologies de linézolide afin d'atteindre la cible d' $AUC_{0-24}/CMI \geq 80$  a consisté à tester l'augmentation de la dose unitaire (1200 mg) ou l'augmentation de la fréquence des doses (600 mg/8h). En effet, ces deux stratégies permettent d'augmenter l'exposition à la molécule de façon satisfaisante.

**Conclusion : Il existe une grande variabilité PK du linézolide dans la population de patients en choc septique sous EERc. La CMI de la bactérie incriminée et les caractéristiques du patient (poids corporel, sévérité) sont des facteurs de risque de doses inappropriées de linézolide, plus que la technique d'EERc utilisée. Des posologies plus élevées (900 mg/12h) pourraient être envisagées mais elles devraient être couplées avec un monitoring des concentrations plasmatiques afin de surveiller le risque de toxicité.**

Article 4 : Analyse PK de population du linézolide dans une population de patients septiques sous CVVH vs CVVHDF. *JAC*, rang A, impact factor 2016 : 5,07.<sup>86</sup>

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Population pharmacokinetics of linezolid in critically ill patients on renal replacement therapy: comparison of equal doses in continuous venovenous haemofiltration and continuous venovenous haemodiafiltration

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**Objectives:** Few data are available to guide linezolid dosing during renal replacement therapy. The objective of this study was to compare the population pharmacokinetics of linezolid during continuous venovenous haemofiltration (CVVHF, 30 mL/kg/h) and continuous venovenous haemodiafiltration (CVVHDF, 15 mL/kg/h + 15 mL/kg/h).

**Methods:** Patients requiring linezolid 600 mg iv every 12 h and CVVHF or CVVHDF were eligible for this prospective study. Seven blood samples were collected over one dosing interval and analysed by a validated chromatographic method. Population pharmacokinetic analysis was undertaken using Pmetrics. Monte Carlo simulations evaluated achievement of a pharmacodynamics target of an AUC from 0–24 h to MIC (AUC<sub>0–24</sub>/MIC) of 80.

**Results:** Nine CVVHDF and eight CVVHF treatments were performed in 13 patients. Regimens of CVVHDF and CVVHF were similar. A two-compartment linear model best described the data. CVVHDF was associated with a 20.5% higher mean linezolid clearance than CVVHF, without statistical significance ( $P=0.39$ ). Increasing patient weight and decreasing SOFA score were associated with increasing linezolid clearance. The mean (SD) parameter estimates were: clearance (CL), 3.8 (2.2) L/h; volume of the central compartment, 26.5 (10.3) L; intercompartmental clearance constants from central to peripheral, 8.1 (12.1) L/h; and peripheral to central compartments, 3.6 (4.0) L/h. Achievement of pharmacodynamic targets was poor for an MIC of 2 mg/L with the studied dose.

**Conclusions:** During CVVHF and CVVHDF, there is profound pharmacokinetic variability of linezolid. Suboptimal achievement of therapeutic targets occurs at the EUCAST breakpoint MIC of 2 mg/L using 600 mg iv every 12 h.

## Introduction

Linezolid is commonly used for difficult-to-treat Gram-positive infections. As linezolid has time-dependent activity, the percentage of time that plasma concentrations exceed the MIC and the AUC over 24 h divided by the MIC (AUC<sub>0–24</sub>/MIC) best describe its efficacy.<sup>1</sup> A higher success rate was reported when plasma concentrations remain above the MIC for the entire dosing interval and when AUC<sub>0–24</sub>/MIC values were 80–120.<sup>2</sup> In the ICU, one-third of patients are admitted for sepsis. Among them, one half of these patients will develop acute kidney injury (AKI) and one half of these will require renal replacement therapy (RRT).<sup>3</sup> Both

sepsis and RRT can alter the pharmacokinetics of many antibiotics due to changes in volume of distribution, increased or decreased clearance and pathophysiological manifestations such as hypoalbuminaemia.<sup>4–6</sup> Previous studies have already reported large variations in peak serum concentrations and AUC<sub>0–24</sub> in ICU patients without RRT treated with linezolid.<sup>7,8</sup> During RRT, data about the pharmacokinetics of linezolid are poorly available and conflicting results are reported. In intermittent haemodialysis (IHD), Swoboda *et al.* reported a high variability in linezolid concentration–time profiles and subtherapeutic concentrations associated with an increased clearance (+3.5 L/h) due to haemodialysis.<sup>9</sup> In a study including 20 ICU anuric patients undergoing continuous

venovenous haemofiltration (CVVHF), Meyer et al. reported that the pharmacokinetics of linezolid were comparable to those in healthy subjects without renal impairment.<sup>10</sup> The ultrafiltration rates used in that study (30 mL/kg/h) were similar to those used in our study. In a similar study (15 ICU patients), the serum concentrations of linezolid decreased below the therapeutic range following IHD, sustained low-efficiency dialysis or CVVHF.<sup>11</sup> The mean amount of the administered dose of linezolid removed was 32.3% during IHD, 33.9% during sustained low-efficiency dialysis and 12.4%–17.5% during CVVHF. Continuous venovenous haemodiafiltration (CVVHDF) has only been studied in two case reports.<sup>12,13</sup> CVVHF and CVVHDF are the most common types of continuous RRT used and are commonly used at a recommended dose of 30 mL/kg/h effluent rate.<sup>3,14</sup> No study has compared the impact of each technique on linezolid pharmacokinetics at a standardized dose of 30 mL/kg/h.

The aim of this study was to compare the population pharmacokinetics of linezolid during equal dosing in CVVHF (30 mL/kg/h) and CVVHDF (15 mL/kg/h + 15 mL/kg/h). We then sought to perform Monte Carlo dosing simulations to determine doses that best achieve pharmacodynamics targets for these patients.

## Materials and methods

### Setting

The study was performed in a tertiary referral ICU (26 beds). It was ancillary to a trial comparing the impact of CVVHF (30 mL/kg/h) and CVVHDF (15 mL/kg/h + 15 mL/kg/h) on the urea reduction rate after 12 h (clinicaltrials.gov NCT 01403220). The local ethics committee of Nîmes (Comité de Protection des Personnes Sud Méditerranée III 2012.02.05) approved the present study. Written informed consent was obtained from either the patient or their nominated substitute decision-maker.

### Study population

Patients were included when they required CVVHF (30 mL/kg/h) or CVVHDF (15 mL/kg/h + 15 mL/kg/h) for AKI and treatment with linezolid for a documented or suspected difficult-to-treat Gram-positive infection. Excluded patients were those in whom the indication for RRT was cardiogenic pulmonary oedema, metabolic acidosis ( $\text{pH} < 7.15$ ,  $\text{HCO}_3^- < 12$  mmol/L) or hyperkalaemia  $> 6.5$  mmol/L and patients with a history of allergy to linezolid.

### RRT

All patients were included in the primary study comparing CVVHF (30 mL/kg/h) and CVVHDF (15 mL/kg/h + 15 mL/kg/h). When a patient was included in the primary study, CVVHF or CVVHDF were alternately used in the same patient but the first therapy was randomly assigned. According to KDIGO guidelines (<http://kdigo.org/home/guidelines/acute-kidney-injury/> Chap 4.5 to 5.8 p87–113) CVVHF and CVVHDF were performed using an Aquarius system (Nikiso, Japan). A polysulfone-type haemofilter with a surface of 1.2 m<sup>2</sup> (Aquamax 12) was always used. RRT was performed via jugular or femoral 14 French double-lumen catheters. The fluid (Phoxilium, Gambro Hospal, France) reinfusion rate was 30 mL/kg/h for CVVHF and 15 mL/kg/h + 15 mL/kg/h dialysate flow rate for CVVHDF. Only the post-dilution technique (i.e. the reinfusion of fluid to compensate ultrafiltrate production is administered after the haemofilter) was applied. According to patient fluid balance assessed by the physician in charge, the net removal fluid was between 0 and 200 mL/h. The targeted flow rate was aimed at providing a filtration ratio  $< 20\%$ . Finally, all circuits were anticoagulated with heparin (200–1000 IU/h) for targeted anti-Xa activity  $> 0.20$ .

### Study protocol

Intravenous linezolid (600 mg) was administered as a 60 min infusion twice a day as part of the patient's prescribed therapy. Pre-filter blood samples to determine plasma linezolid concentrations were taken at baseline (H0), at the end of infusion (H1), 1.5 (H1.5), 2 (H2), 4 (H4), 8 (H8) and 12 h (H12) after the end of infusion just before the subsequent dose. Post-filter blood samples were taken at 1.5 (H1.5), 2 (H2), 8 (H8) and 12 h (H12) after the end of linezolid infusion. For blood samples, 3 mL was withdrawn in a lithium heparin tube.

### Measured patient parameters

The following parameters were collected for all enrolled patients:

- Demographic characteristics: age, sex, height and weight with calculated body mass index
- Medical history, initial reason for ICU admission and Simplified Acute Physiology Score II (SAPS II)<sup>15</sup> at ICU admission.
- Clinical parameters: urine output was classically collected every 2 h. The SOFA<sup>16</sup> score was also collected.
- Type of infection and anti-infective therapy: type of infection; anti-infective agents administered; and microbiological cultures collected.
- Measured renal replacement modalities: For each session of CVVHDF or CVVHF, the blood flow rate, ultrafiltrate volume and effective time of RRT were recorded.

### Sample handling, storage and measurement

Blood samples were immediately placed on ice and centrifuged within 60 min at 3000 rpm, for 10 min then stored at  $-80^\circ\text{C}$ . Samples were transported by a commercial courier company to the Burns, Trauma & Critical Care Research Centre, The University of Queensland, for analysis. An HPLC-UV assay was used to measure linezolid concentrations in plasma. All bioanalysis techniques were validated and conducted in accordance with criteria of the US FDA guidance for industry on bioanalysis (available at: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf)).

### Population pharmacokinetic modelling

Two- and three-compartment models were developed with the Nonparametric Adaptive Grid (NPAG) algorithm within the freely available software Pmetrics package for R (Los Angeles, CA, USA).<sup>17,18</sup> Elimination from the central compartment and intercompartmental distribution into the peripheral or other compartments were modelled as first-order processes using differential equations. AUC from 0 to 24 h ( $\text{AUC}_{0-24}$ ) was calculated using Pmetrics. Demographic and clinical characteristics that were considered biologically plausible for affecting linezolid pharmacokinetics, were tested for inclusion as covariates. If inclusion of the covariate resulted in a statistically significant improvement in the log likelihood ( $P < 0.05$ ) and/or improved the goodness of fit plots, then it was supported for inclusion.

### Model diagnostics

The goodness of fit was assessed by visual inspection of the observed–predicted plot, coefficient of determination of the linear regression of the observed–predicted values and log-likelihood values from each run. Predictive performance evaluation was based on mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models.

### Probability of target attainment

Monte Carlo simulations ( $n = 1000$ ) were employed using Pmetrics to determine the probability of target attainment (PTA) of achieving an  $\text{AUC}/\text{MIC} \geq 80$  for varying MICs (0.5–4 mg/L) during the first 24 h of

treatment for a patient with a SOFA score of 13, and a total body weight of 60 kg, 90 kg and 120 kg.

### Fractional target attainment calculation

MIC data for *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium* and CoNS from the EUCAST database (available at [www.eucast.org](http://www.eucast.org)) were used to determine fractional target attainment. The fractional target attainment identifies the likely success of treatment by comparing the pharmacodynamic exposure (PTA) against MIC distribution. The fractional target attainment was calculated using  $AUC/MIC \geq 80$ . The PTA for achieving  $AUC/MIC \geq 80$  was calculated for the Monte Carlo simulations ( $n=1000$ ) for various doses: 600 mg iv every 24 h, 1200 mg iv every 24 h, 600 mg iv every 12 h and 900 mg iv every 12 h during the first 24 h of therapy. A priori, a dosing regimen was considered successful if the fractional target attainment was  $>85\%$ .

### Statistical analysis

Continuous data are presented as the mean (SD) or median (IQR). Categorical data are presented as counts (%). Comparisons used Mann-Whitney and  $\chi^2$  tests as appropriate. Correlation was assessed by means of a scatter graph and Pearson correlation coefficient ( $r$ ). Differences in linezolid clearance by CVVHF and CVVHDF were analysed using a Student's  $t$ -test.  $P < 0.05$  was considered statistically significant, and all analyses were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA).

## Results

### Patients, infections and pathogens

Fifteen included patients provided consent but blood samples were unable to be taken in two patients. Therefore, data of 13 patients with severe sepsis were available for analysis (Table 1). Among them, 11 required vasopressor support (10 with noradrenaline, 1 with noradrenaline and dobutamine). The source of infection was pulmonary (four), abdominal (six) and blood (three). Antibiotics including linezolid were always empirically initiated. No pathogen was isolated in three (23%) patients whereas multiple pathogens were isolated in eight (61%). Bacteriological samples showed nine Gram-positive (seven *Staphylococcus aureus*, two *Enterococcus*) and eight Gram-negative (three *Escherichia coli*, two *Klebsiella pneumoniae*, one *Enterobacter cloacae*, one *Serratia marcescens*, one *Morganella morganii*) pathogens, respectively. The MIC for Gram-positive pathogens was always 2 mg/L. Among the 13 included patients, 7 (53%) died in ICU.

### RRT therapy

Four patients underwent both CVVHDF and CVVHF whereas CVVHF and CVVHDF were performed solely in four and five patients, respectively. Therefore, linezolid pharmacokinetics was studied during nine and eight CVVHDF and CVVHF treatment sessions, respectively. The comparison between CVVHDF and CVVHF sessions is shown in Table 2. At baseline, the time of initiation of the sampling from admission and RRT initiation, patient severity, diuresis in the last 12 h period, mean arterial pressure, serum creatinine and uraemia were similar. These parameters remained similar after 12 h of CVVHDF or CVVHF.

### Pharmacokinetics of linezolid

The observed mean linezolid concentration-time profile is shown in Figure 1. A two-compartment linear model best described the

**Table 1.** Demographic, anthropometric and illness severity data on the 13 included patients

Descriptive data	n or median (IQR)
Female/male	5/8
Age (years)	72 (61–72)
Weight (kg)	76 (55–92)
Height (cm)	165 (153–178)
BMI (kg/m <sup>2</sup> )	24 (23–34)
Comorbidities	
hypertension	7
coronary artery disease	1
COPD	4
cirrhosis	2
non-dialysis chronic renal disease	2
SAPS II at admission	52 (49–62)
SOFA at admission	12 (10–13)
time between admission and RRT initiation (days)	1 (0–2)
SOFA at RRT initiation	13 (11–17)
time (h) between RRT initiation and studied RRT	0 (0–1)
serum creatinine at studied RRT initiation ( $\mu$ M)	221 (142–249)
uraemia at studied RRT initiation (mM)	20 (8–24)
protein at studied RRT initiation (g/L)	41 (39–47)
anti-Xa activity at studied RRT initiation (IU)	0.10 (0.00–0.13)

COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiology score.

data. The model was considered acceptable according to the goodness of fit evaluations (Figure 2). CVVHDF was associated with a 20.5% higher mean linezolid clearance than CVVHF, although the difference was not significant (5.9 versus 4.5 L/h,  $P=0.39$ ). Both increasing patient weight and decreasing SOFA score were associated with increasing drug clearance and were supported as covariates in the final model. The mean (SD) parameter estimates were clearance (CL) 3.8 (2.2) L/h, volume of the central compartment ( $V_{\text{central}}$ ) 26.5 (10.3) L, intercompartmental clearance constants from central to peripheral (kcp) 8.1 (12.1) L/h and peripheral to central compartments (kpc) 3.6 (4.0) L/h (Table 3). The mean  $AUC_{0-24}$  was 227.9 (115.0) mg-h/L.

### Dosing simulations

Figure 3 presents the dosing simulations for various doses and their PTA for achieving an  $AUC/MIC \geq 80$  for varying MICs (0.5–4 mg/L) during the first 24 h of treatment for a patient with a SOFA score of 13, and a total body weight of 60 kg, 90 kg and 120 kg. These data confirm that increasing patient weight and increasing MIC were associated with a reduced PTA. Using the studied dose, 94% of patients achieve a therapeutic  $AUC_{0-24}/MIC$  for an MIC of 1 mg/L, 69% for 2 mg/L and 24% for 4 mg/L.

### Fractional target attainment

The fractional target attainment for the simulated PTAs for a range of linezolid doses, dose frequencies and patient weights against the MIC distribution for four different Gram-positive

**Table 2.** Characteristics of RRT session<sup>a</sup>

Parameters	CVVHDF (n=9)	CVVHF (n=8)	P value
<b>Baseline</b>			
time between admission to RRT session (days)	1 (0–2)	4 (1–13)	0.1
number of RRT sessions per patient	1 (1–2)	2 (1–4)	0.2
SOFA at initiation of RRT session	13 (6–17)	12 (10–16)	0.98
diuresis over previous 12 h period (mL)	210 (90–467)	102 (30–652)	0.7
mean arterial pressure (mmHg)	77 (75–82)	89 (63–98)	0.5
serum creatinine ( $\mu$ M)	234 (200–290)	180 (97–294)	0.3
uraemia (mmol/L)	20 (12–32)	12 (7–23)	0.2
protein (g/L)	41 (38–47)	44 (36–55)	0.7
anti-Xa activity	0.06 (0–0.18)	0.06 (0.01–0.13)	0.95
<b>After 12 h of RRT</b>			
diuresis (mL/kg/h)	0.1 (0.0–0.25)	0.05 (0.0–0.55)	0.6
mean arterial pressure (mmHg)	80 (77–86)	80 (63–87)	0.5
serum creatinine ( $\mu$ M)	154 (126–195)	144 (98–188)	0.5
uraemia (mM)	13 (8–18)	11 (6–14)	0.4
protein (g/L)	44 (39–51)	43 (40–60)	0.6
<b>RRT session parameters</b>			
arterial pressure (mmHg)	–30 (–57 to –6)	–37 (–70–27)	0.9
trans-membrane pressure (mmHg)	39 (29–58)	63 (19–88)	0.5
venous return pressure (mmHg)	89 (76–105)	101 (81–115)	0.4
blood flow rate (mL/min)	200 (165–200)	200 (185–245)	0.5
fluid removal (mL)	1100 (360–1630)	3620 (190–4270)	0.48
reinfusion flow rate (mL/kg/h)	16 (13–17)	22 (22–23)	NA
dialysis flow rate (mL/kg/h)	15 (15–17)	NA	NA
filtration fraction (%)	12 (9–15)	17 (12–18)	0.07
actual time of RRT (min)	745 (645–733)	715 (697–751)	0.6
effective time of RRT (% total RRT time)	100 (95–100)	97 (94–98)	0.16

NA, not applicable.

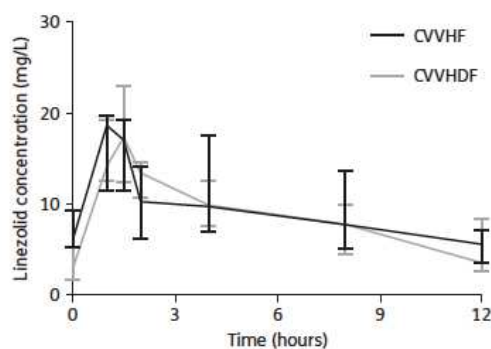
<sup>a</sup>Data are expressed as median [IQR].

pathogens is shown in Table 4. These data show that doses >600 mg every 12 h are mostly required for all patient weights with larger decreases in fractional target attainment seen with increasing patient weight.

## Discussion

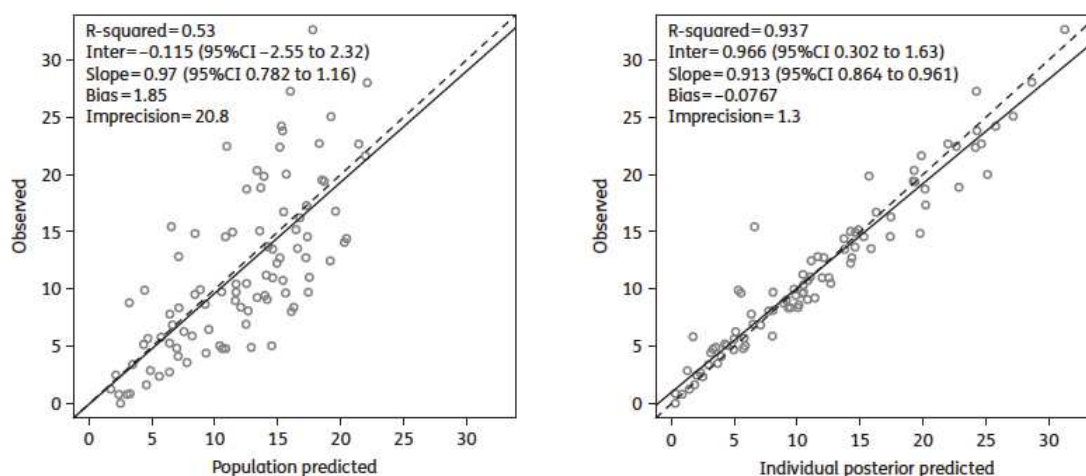
The present study compared the pharmacokinetics of 600 mg iv linezolid every 12 h given during CVVHDF (15 mL/kg/h+15 mL/kg/h) or CVVHF (30 mL/kg/h) in ICU patients with severe sepsis and AKI. Between CVVHDF and CVVHF, there was no statistically significant difference in linezolid clearance. However, the present data highlight the profound pharmacokinetic variability of linezolid during CVVHF and CVVHDF with patient weight and sickness severity most prominently influencing drug disposition. The importance of weight is likely manifest in the weight-based RRT dose. Suboptimal achievement of therapeutic targets occurs at the EUCAST breakpoint MIC of 2 mg/L using conventional 600 mg iv every 12 h.

When AKI occurs requiring RRT, these pathophysiological and treatment changes can lead to difficult-to-predict linezolid pharmacokinetics due to the different RRT modalities and the



**Figure 1.** The mean concentration–time profiles for the dosing interval of linezolid sampling in critically ill patients receiving CVVHF or CVVHDF. Error bars represent standard deviations.

different settings used with each technique.<sup>3,19,20</sup> In 2004, Fiaccadori et al. reported subtherapeutic concentrations of linezolid following conventional IHD, sustained low-efficiency dialysis or CVVHF in 15 critically ill patients with AKI.<sup>11</sup> In contrast, Meyer



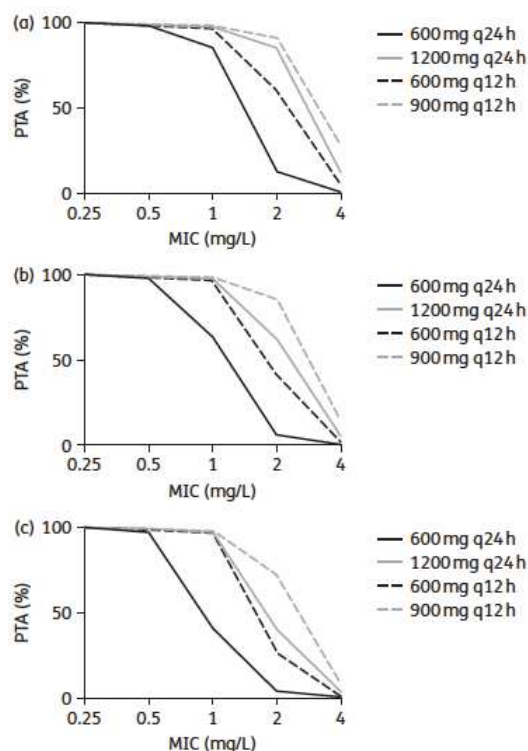
**Figure 2.** Diagnostic plots for the final covariate model. Observed versus population predicted concentrations (left panel) and individual predicted concentrations (right panel) in plasma. Data are presented in mg/L.

**Table 3.** Parameter estimates for linezolid from the final covariate two-compartment population pharmacokinetic model

Parameter	Mean	Standard deviation	Coefficient of variation	Median
CL (L/h)	3.8	2.3	61.3	3.1
$V_{central}$ (L)	26.5	10.7	40.5	30.8
$k_{cp}$ ( $h^{-1}$ )	8.1	12.5	153.6	0.6
$k_{pc}$ ( $h^{-1}$ )	3.6	4.2	117.1	0.6

CL, clearance;  $k_{cp}$ , rate constant for drug distribution from the central to peripheral compartment;  $k_{pc}$ , rate constant for drug distribution from the peripheral to central compartment;  $V_{central}$ , volume of distribution of the central compartment.

*et al.* did not report any difference in the pharmacokinetics of linezolid in 20 patients requiring CVVHF.<sup>10</sup> In these previous studies, RRT settings used were not standardized leading to potentially erroneous conclusions. In the present study, two techniques of RRT were compared with similar RRT settings used throughout the study period. As expected, only reinfusion flow rate, dialysis flow rate and filtration fraction were different between CVVHDF and CVVHF. When comparing these two techniques, no statistical difference in pharmacokinetics was observed even though the mean linezolid clearance was 20.5% higher with CVVHDF. However, due to the small number of patients included in this study, we cannot confirm that these two techniques provide similar linezolid clearance. In clinical practice, the present study shows that pharmacokinetics of 600 mg iv every 12 h linezolid is similar in CVVHDF (15 mL/kg/h + 15 mL/kg/h) or CVVHF (30 mL/kg/h). The calculated  $V_{central}$  in the present study (26.5 L) is consistent with  $V_{central}$  reported in healthy volunteers.<sup>21</sup> Great variability of volume of distribution ( $V_d$ ) has been reported in patients undergoing



**Figure 3.** Monte Carlo simulations and probability of target attainment in plasma for various linezolid doses for body weights: (a) 60 kg, (b) 90 kg, (c) 120 kg.

**Table 4.** Fractional target attainment for the various linezolid doses for a patient with a SOFA score of 13 and body weights of 60 kg, 90 kg or 120 kg for an *E. faecalis*, *E. faecium*, CoNS and *S. aureus* MIC distribution

Body weight, iv dose and frequency	Fractional target attainment (%) <sup>a</sup>			
	<i>E. faecalis</i>	<i>E. faecium</i>	CoNS	<i>S. aureus</i>
<b>60 kg</b>				
600 mg every 24 h	50.8	42.0	67.5	37.6
1200 mg every 24 h	<b>88.5</b>	<b>87.1</b>	<b>93.6</b>	<b>85.0</b>
600 mg every 12 h	76.6	72.5	<b>86.7</b>	69.3
900 mg every 12 h	<b>92.0</b>	<b>91.3</b>	<b>95.5</b>	<b>89.6</b>
<b>90 kg</b>				
600 mg every 24 h	37.4	30.8	51.4	26.3
1200 mg every 24 h	77.9	73.7	<b>87.9</b>	70.6
600 mg every 12 h	67.9	61.5	81.9	57.6
900 mg every 12 h	<b>88.8</b>	<b>87.5</b>	<b>93.8</b>	<b>85.4</b>
<b>120 kg</b>				
600 mg every 24 h	26.2	22.5	36.2	18.1
1200 mg every 24 h	68.1	61.5	82.4	57.5
600 mg every 12 h	62.1	53.8	79.2	49.4
900 mg every 12 h	<b>82.5</b>	75.6	<b>90.4</b>	76.9

<sup>a</sup>Doses achieving the a priori target of PTA against at least 85% of isolates are shown in bold.

CVVHF. Meyer et al. showed  $V_d$  varying from 29.9 L to 70.7 L.<sup>10</sup> Moreover, Swoboda et al. reported in critically ill patients low  $V_{central}$  (0.27 L/kg).<sup>9</sup>

Previous studies focused on the pharmacokinetics of linezolid in ICU patients reported a great variability in peak serum concentrations and AUC.<sup>22–24</sup> The variability could be explained by changes in  $V_d$ , protein binding and clearance in ICU patients.<sup>6</sup> Consistent with these previous studies, we observed a great variability in the present study regardless of the type of RRT used (Figure 2). These findings led to a low achievement of pharmacodynamics targets for an MIC of 2 mg/L with 600 mg iv every 12 h. Therefore, subtherapeutic serum concentrations could be suspected with this dosing particularly when the patient weight is >90 kg and/or when MIC is high (4 mg/L), which could increase the likelihood of clinical failure or emergence of microbial resistance. Further, increased dosing in such patients could expose patients to side effects associated with linezolid. Thrombocytopenia has been reported particularly in patients with renal dysfunction.<sup>25</sup> Therefore, the present study supports use of linezolid serum concentration monitoring in ICU patients with severe sepsis requiring RRT. All these findings demonstrate that the characteristics of patients with severe sepsis and the MIC of the pathogen are more important determinants of achievement of therapeutic serum concentrations of linezolid than modalities of RRT.

The present study has several limitations. The study was underpowered to conclude definitively that these regimens of CVVHF and CVVHDF are not associated with statistical difference in pharmacokinetics in 600 mg iv 12-hourly linezolid. This study is a substudy of an on-going cross-over randomized controlled clinical outcome trial of CVVHF and CVVHDF. Despite this, only four patients achieved cross-over (i.e. received both CVVHF and

CVVHDF). The nine remaining patients received either CVVHF (four patients) or CVVHDF (five patients). We could not assess mechanistically if the subtherapeutic concentrations observed were caused by RRT or non-RRT clearance because the disposition of linezolid into RRT effluent was not determined. We did not standardize the linezolid pharmacokinetic analysis regarding the number of received doses and the beginning of RRT. The filter life was standardized to a 72 h life except clotting that could reduce the filter life, although the age of the filter was not standardized with respect to commencement of linezolid or sampling.

Finally, the present study was not designed to measure any difference in patient outcome such as clinical infection cure or survival.

## Conclusions

The present data indicate profound pharmacokinetic variability of linezolid during CVVHF and CVVHDF. Suboptimal achievement of therapeutic targets occurs at the EUCAST breakpoint MIC of 2 mg/L using 600 mg iv every 12 h.

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## Transparency declarations

None to declare.

## Author contributions

C. R. participated in the design of the study, collecting patient data, analysing the data and writing the paper. L. M. participated in the design of the study, collecting patient data, analysing the data and writing the paper. S. C. W. participated in performing plasma concentration dosages and analysing the data. B. L. participated in the design of the study, performing the statistical analysis, analysing the data and writing the paper. G. S. participated in collecting and analysing the data. J. L. participated in analysing the data and was senior advisor. J. Y. L. participated in the design of the study, collecting and analysing the data, and writing the paper. J. A. R. participated in the design of the study, analysing the data and writing the paper. All authors read and approved the final manuscript.

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**Article 5 : Analyse PK de population de la ciprofloxacine dans une population de patients en choc septique : comparaison CVVH vs CVVHDF. JAC, rang A, impact factor 2016 : 5,07.<sup>90</sup>**

La ciprofloxacine appartient à la classe des fluoroquinolones, fréquemment prescrites pour traiter des infections à bacilles Gram négatif (BGN) résistants tels que *P.aeruginosa*. Elle présente un profil PK favorable du fait de son large Vd et sa bonne diffusion tissulaire notamment dans l'os. Cependant, l'usage de cet antibiotique est responsable de l'émergence de résistance bactérienne, en particulier de *Staphylococcus aureus* méthicilline résistant (SARM).<sup>91</sup> L'utilisation de posologies adaptées est donc un enjeu majeur pour cette classe d'antibiotique. Son activité bactéricide est temps et concentration dépendante. Une AUC/CMI  $\geq 125$  est définie comme le critère PK/PD le mieux corrélé à la guérison clinique.<sup>92</sup> Dans ce travail, plusieurs modèles structuraux ont été testés. Un modèle bi-compartimental a été retenu pour décrire les données PK représentées par 141 prélèvements plasmatiques obtenus auprès de 8 patients sous CVVHDF et 10 patients sous CVVH. L'analyse des covariables a permis d'identifier le poids corporel réel comme facteur affectant la PK de la ciprofloxacine dans la population d'étude. En d'autres mots, l'augmentation de clairance de ciprofloxacine est corrélée à un poids croissant. L'analyse des concentrations individuelles dites postérieures ne met pas en évidence de différence statistiquement significative concernant les clairances obtenues entre les différentes modalités d'EERc : la clairance moyenne de la ciprofloxacine dans le groupe CVVH est de  $11,8 \pm 9,9$  L/h comparée à  $10,3 \pm 7,4$  L/h dans le groupe CVVHDF ( $p=0,43$ ). Ces résultats sont concordants avec les données de Wallis et al. Qui rapportaient une clairance totale de  $10,7 \pm 5,3$  L/h soit une clairance extra-corporelle fractionnelle de 21%.<sup>93</sup> Les MCS ont permis de tester plusieurs schémas posologiques de dose unitaire et de fréquence

d'administration. Les AUC simulées ont été rapportés à différentes valeurs de CMI afin de calculer la probabilité d'atteindre la cible  $AUC/CMI \geq 125$  avec les différents schémas posologiques en fonction de la sensibilité des germes. De plus, la distribution des CMI des germes les plus fréquemment traités par ciprofloxacine (*P.aeruginosa*, *Escherichia coli*, *A.baumannii* et *Klebsiella pneumoniae*) a été confrontée aux AUC estimées pour les différents schémas posologiques. L'analyse des MCS a mis en évidence que le schéma d'administration de 400 mg/8 heures de ciprofloxacine serait le schéma optimal pour atteindre la cible PK/PD lorsque la ciprofloxacine est administrée pour traiter des germes de sensibilité diminuée ou pour les patients avec un poids  $\geq 90$  kg dans la population de patients sous EERc quelque soit le mode appliqué.

**Conclusion : Ce travail démontre, à doses d'EER équivalentes, que la technique d'EER influence peu la PK de la ciprofloxacine. Le type de pathogène à traiter et surtout la susceptibilité de ce pathogène serait le facteur principal déterminant l'adaptation posologique dans cette population de patients de réanimation sous EERc. Des posologies de 400 mg/8 heures doivent être envisagées pour traiter les germes tels que *P. aeruginosa* et *A. baumannii* ainsi que pour les patients avec un poids  $\geq 90$  kg.**

Article 5 : Analyse PK de population de la ciprofloxacine dans une population de patients septiques sous CVVH vs CVVHDF. *JAC*, rang A, impact factor 2016 : 5,07.<sup>90</sup>

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Comparison of equal doses of continuous venovenous haemofiltration and haemodiafiltration on ciprofloxacin population pharmacokinetics in critically ill patients

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**Objectives:** Whilst commonly performed in ICUs, renal replacement therapies (RRTs) differ in their solute clearances. There is a paucity of data on ciprofloxacin clearances in different RRT techniques. The aim of this study was to compare the population pharmacokinetics of ciprofloxacin during equal doses of continuous venovenous haemofiltration (CVVHF) and continuous venovenous haemodiafiltration (CVVHDF) in septic patients.

**Methods:** Patients receiving 400 mg of ciprofloxacin intravenously 8 or 12 hourly and undergoing either CVVHF or CVVHDF were eligible. Up to 10 blood samples were collected over one dosing interval and analysed by a validated chromatographic method. Population pharmacokinetic analysis and Monte Carlo simulation was undertaken using Pmetrics.

**Results:** Eighteen sampling intervals were included (8 CVVHDF and 10 CVVHF) from 11 patients (6 patients having sampling during both RRT modes). A two-compartment linear model best described the data. Increasing patient weight was the only covariate associated with increasing drug clearance. The mean (SD) parameter estimates were: clearance, 10.7 (5.3) L/h; volume of distribution of the central compartment, 21.3 (11.3) L; rate constant for drug distribution from the central compartment to the peripheral compartment, 10.9 (4.3) L/h; and rate constant for drug distribution from the peripheral compartment to the central compartment, 2.3 (1.8) L/h. After accounting for patient weight, the mean ciprofloxacin clearance was not statistically different between CVVHF and CVVHDF [11.8 (9.9) and 10.3 (7.4) L/h, respectively,  $P=0.43$ ].

**Conclusions:** The present study indicates a high pharmacokinetic variability of ciprofloxacin during CVVHF and CVVHDF with no significant differences in clearance apparent. Based on patient weight, higher ciprofloxacin dosing regimens should be used in critically ill patients when difficult-to-treat pathogens are suspected.

## Introduction

In ICU, acute kidney injury (AKI) is an independent risk factor of poor outcome in patients with severe sepsis.<sup>1</sup> Appropriate antimicrobial therapy and organ failure support are two main objectives for improving patient outcome.<sup>2</sup> However, giving the optimal antibiotic dosing regimen for critically ill patients undergoing renal replacement therapy (RRT) remains a difficult challenge for clinicians.<sup>3</sup> It is well known that many factors such as hypoalbuminaemia, increased volume of distribution and decreased or increased renal clearance influence antibiotic concentrations in

critically ill patients.<sup>4,5</sup> Moreover, continuous modes of RRT (CRRT) [continuous venovenous haemofiltration (CVVHF) and continuous venovenous haemodiafiltration (CVVHDF)] are widely used in ICUs to treat AKI but the influence of these different RRT modes on drug clearance is not well described. Theoretically, the physicochemical process (convection and/or diffusion), membrane surface area, mode of replacement fluid administration (pre- or post-dilution) and ultrafiltration and/or dialysate flow rates applied could directly influence the extent of drug removal by CRRT clearance.<sup>6</sup> This could lead to antibiotic underdosing associated with both therapeutic failure and resistance

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emergence risks. Therapeutic drug monitoring (TDM) could be extremely useful but is not routinely available in most ICUs.<sup>7,8</sup>

Previous studies have already reported a large variability in ciprofloxacin plasma concentrations in critically ill patients<sup>9–12</sup> but few data are available to guide the ciprofloxacin dosing regimen during CRRT.<sup>13–15</sup> The influence of the mode of RRT on ciprofloxacin pharmacokinetics using standardized RRT settings has never been studied in critically ill patients.

The aim of the present study was to compare the influence of CVVHF and CVVHDF on ciprofloxacin pharmacokinetics using similar membrane surface area, post-dilution replacement fluid and equal doses of RRT. Then, we aimed to use Monte Carlo dosing simulations to describe doses associated with the achievement of pharmacodynamic targets and determine the optimal dosage adjustment in these patients.

## Methods

### Setting

This was an observational pharmacokinetic study using convenient sampling at a tertiary referral ICU. It was an ancillary part of a randomized trial comparing the effect of equal doses of CVVHF (30 mL/kg/h) and CVVHDF (15 mL/kg/h + 15 mL/kg/h) on the urea reduction rate after a 12 h period (ClinicalTrials.gov NCT 01403220).<sup>16</sup> The primary study is completed but is as yet unpublished.

### Ethics

Ethics approval was obtained from the local ethics committee of Nîmes (Comité de Protection des Personnes Sud Méditerranée III 2012.02.05). Written informed consent was obtained from either the patient or their nominated substitute decision-maker.

### Study population

The inclusion criteria for this study were: (i) AKI defining according to the RIFLE criteria<sup>17</sup> and necessitating CRRT; and (ii) clinical indication for ciprofloxacin use.

The exclusion criteria were: (i) requirement of RRT for cardiogenic pulmonary oedema, metabolic acidosis ( $\text{pH} < 7.15$ ,  $\text{HCO}_3^- < 12$  mmol/L) or hyperkalaemia  $> 6.5$  mmol/L; and (ii) patients with a history of allergy or contraindication to ciprofloxacin.

Where possible, patients that randomly received both CVVHF and CVVHDF at different times of their antibiotic therapy were included.

### RRT

All patients were included in the primary study comparing equal doses of CVVHF (30 mL/kg/h) and CVVHDF (15 + 15 mL/kg/h) based on total body weight. Both types of RRT (CVVHF or CVVHDF) were alternatively used in the same patient but the first therapy session was randomly allocated. Both techniques of RRT were performed using an Aquarius system (Nikiso, Japan). A polysulfone-type haemofilter with a surface of 1.9 m<sup>2</sup> (Aquamax HF19) was systematically used, such as jugular or femoral 14 French double-lumen catheters. The RRT settings were:

- (i) A 30 mL/kg/h fluid (Phoxilium, Gambro Hospital, France) reinfusion rate for CVVHF and a 15 mL/kg/h (reinfusion rate) + 15 mL/kg/h dialysate flow rate for CVHDF. For both techniques, we used the post-dilution mode.
- (ii) The net removal fluid rate was left to the physician's discretion and was set up between 0 and 200 mL/h.
- (iii) The targeted blood flow rate was aimed at providing a filtration ratio  $< 20\%$ . The filtration ratio was calculated as follows: filtration ratio = ultrafiltrate flow rate/blood flow rate.

- (iv) All circuits were anti-coagulated with heparin (200–1000 IU/h) for a targeted anti-Xa activity  $> 0.20$ .

### Study protocol

Four-hundred milligrams of intravenous (iv) ciprofloxacin was administered as a 60 min infusion either 8 or 12 hourly as part of the patient prescribed antimicrobial therapy in combination with a  $\beta$ -lactam when sepsis was suspected according to the Surviving Sepsis Campaign criteria.<sup>2</sup> Pre-filter blood samples to determine plasma ciprofloxacin concentrations were taken at baseline, at the end of infusion (1 h), 1.5, 2, 2.5, 3, 3.5, 4 and 8 (plus an additional sample at 12 h, if 12 hourly dosing) after the start of infusion just before the subsequent dose according to the dose regimen used. Post-filter blood samples were taken at the same times as the pre-filter samples, except no sample was taken at the end of infusion (1 h).

### Patient data collection

Additional clinical and demographic data were collected, including Simplified Acute Physiology Score II (SAPS II)<sup>18</sup> at ICU admission, SOFA<sup>19</sup> score, comorbidities and 28 day outcome, were documented. During the RRT treatment, CVVHF or CVVHDF settings were also recorded. Type of infection, antimicrobial agents administered, microbiological cultures and MIC (if available) were collected.

### Sample handling, storage and measurement

Blood samples were immediately placed on ice and centrifuged within 60 min at 3000 rpm for 10 min then stored at  $-80^\circ\text{C}$ . Samples were transported by a commercial courier company to the Burns Trauma and Critical Care Research Centre, The University of Queensland, Australia, for analysis. Ciprofloxacin concentrations in plasma were determined by HPLC with fluorescence detection on a Shimadzu Prominence instrument. The assay was validated and conducted in accordance with the criteria of the US FDA's guidance for industry on bioanalysis (available at [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf)). The calibration curve was linear with a weighing of  $1/x^2$  over the range 0.1–10 mg/L. The precision and accuracy at the lowest limits of quantification were  $\leq 3.4\%$ . The assay was validated against matrix effects (precision and accuracy within 4.7% at high and low concentrations). The assay's intra-day precision and accuracy was within 8.5% at all three concentrations tested. Storage stability at  $-80^\circ\text{C}$  has been validated for aqueous stocks (15.2 months) and plasma (14.5 months). There was no interference from gentamicin, ceftriaxone, meropenem, doripenem, fluconazole, linezolid, caspofungin, zanamivir, vancomycin or piperacillin.

### Population pharmacokinetic modelling

One- and two-compartment models were developed with the Nonparametric Adaptive Grid algorithm within the freely available Pmetrics software package for R (Los Angeles, CA, USA).<sup>20,21</sup> Elimination from the central compartment and intercompartmental distribution (two-compartment model) into the peripheral compartment were modelled as first-order processes using differential equations.  $\text{AUC}_{0-24}$  was calculated using Pmetrics.

### Model diagnostics

Goodness of fit was assessed by regression, with an observed–predicted plot, coefficients of determination and log-likelihood values. Predictive performance evaluation was based on mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models.

**Probability of target attainment (PTA)**

Monte Carlo simulations ( $n=1000$ ) were employed using Pmetrics to determine the PTA of achieving an  $(AUC_{0-24}/MIC) \geq 125$  for clinically relevant MICs (0.0625–1 mg/L) during the first 24 h of treatment for patients with total body weight of 50, 90 and 140 kg.

**Table 1.** Demographics, anthropometrics and illness severity of 11 included patients

Female/male, $n/n$	3/8
Age (years), median (IQR)	72 (55–77)
Weight (kg) at admission, median (IQR)	70 (60–102)
Height (cm), median (IQR)	168 (154–181)
BMI ( $kg/m^2$ ), median (IQR)	26 (24–35)
Comorbidities, $n$	
hypertension	5
COPD	3
cirrhosis	2
SAPS II at admission, median (IQR)	49 (47–63)
SOFA score at admission, median (IQR)	11 (10–13)

**Fractional target attainment calculation**

MIC data for *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa* from the EUCAST database (available at [www.eucast.org](http://www.eucast.org)) were used to determine fractional target attainment. The fractional target attainment identifies the likely success of treatment by comparing the pharmacodynamic exposure (PTA) against an MIC distribution. The fractional target attainment was calculated using  $AUC_{0-24}/MIC \geq 125$ . The PTA for achieving  $AUC_{0-24}/MIC \geq 125$  was calculated for the Monte Carlo simulations ( $n=1000$ ) for various doses 200 mg intravenous (iv) 12 hourly, 200 mg iv 8 hourly, 400 mg iv 12 hourly, 400 mg iv 8 hourly, 600 mg iv 12 hourly during the first 24 h of therapy. *A priori*, a dosing regimen was considered successful if the fractional target attainment was >85%.

**Statistical analysis**

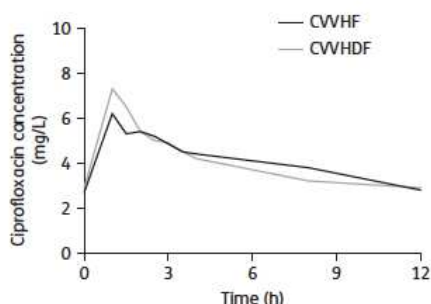
Continuous data are presented as the mean (SD) or median (IQR). Categorical data are presented as counts (%). Comparisons were made using the Mann–Whitney  $U$ -test and the  $\chi^2$  test, as appropriate. Correlation was assessed by means of a scatter graph and Pearson correlation coefficient ( $r$ ). Differences in ciprofloxacin clearance by CVVHF and CVVHDF were analysed using a Student's  $t$ -test.  $P < 0.05$  was considered statistically significant, and all analyses were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA).

**Table 2.** RRT characteristics

Parameter	CVVHDF ( $n=8$ )	CVVHF ( $n=10$ )	$P$
<b>Baseline</b>			
time between admission and RRT session (days)	2.5 (1–18)	10 (2–19)	0.4
time since the beginning of antibiotic therapy (days)	4.5 (3–9)	6.5 (3–8)	0.8
SOFA at the initiation of the RRT session	11 (8.3–13)	11 (9.5–13)	0.8
vasopressor support, $n$ (%)	7 (88)	9 (90)	0.8
diuresis over the previous 12 h period (mL)	243 (0–554)	240 (21–510)	0.8
mean arterial pressure (mmHg)	77 (68–86)	80 (70–91)	0.5
serum creatinine ( $\mu mol/L$ )	237 (206–298)	218 (138–259)	0.4
urea (mmol/L)	14 (12–21)	15 (9.5–23)	0.9
albumin (g/dL)	21 (15.5–23.6)	20 (17.5–22)	0.9
haematocrit (%)	28.6 (25.8–30.4)	27.8 (24.4–30.4)	0.6
<b>After 12 h of RRT</b>			
diuresis (mL/kg/h)	30 (10–620)	65 (10–275)	0.9
mean arterial pressure (mmHg)	77 (73–79)	75 (62–92)	0.7
serum creatinine ( $\mu mol/L$ )	162 (149–168)	154 (123–176)	0.5
urea (mmol/L)	9.2 (6–13)	11 (7.2–15)	0.5
<b>RRT session parameters</b>			
arterial pressure (mmHg)	–33 (–65 to –7)	–75 (–96 to –23)	0.3
trans-membrane pressure (mmHg)	52 (24–72)	80 (50–97)	0.2
venous return pressure (mmHg)	117 (78–133)	117 (86–132)	0.9
blood flow rate (mL/min)	200 (200–200)	250 (200–273)	0.1
fluid removal (mL/day)	640 (103–1593)	1155 (227–1958)	0.5
reinfusion flow rate (mL/kg/h)	19 (13–20)	34 (22–37)	0.026
dialysate flow rate (mL/kg/h)	15 (15–16)	—	—
filtration ratio (%)	12 (8–14)	19 (15–20)	0.009
actual time of RRT (min)	720 (697–720)	697 (631–708)	0.1
effective time of RRT (% total RRT time)	100 (97–100)	97 (94–99)	0.2

Results are expressed as median (IQR), unless otherwise stated.

Comparisons were made using the Mann–Whitney  $U$ -test; statistically significant if  $P < 0.05$ .



**Figure 1.** Observed mean concentration–time profiles for the dosing interval of ciprofloxacin sampling in critically ill patients receiving CVWHF or CVVHDF.

**Table 3.** Parameter estimates for ciprofloxacin from the final covariate two-compartment population pharmacokinetic model

	Mean	SD	Coefficient of variation	Median
Clearance (L/h)	10.7	5.3	49.6	8.5
$V_{central}$ (L)	21.3	11.3	53.2	17.0
$k_{cp}$ (/h)	10.9	4.3	39.6	12.3
$k_{pc}$ (/h)	2.3	1.8	74.8	2.0

$V_{central}$ , volume of distribution of the central compartment;  $k_{cp}$ , rate constant for drug distribution from the central compartment to the peripheral compartment;  $k_{pc}$ , rate constant for drug distribution from the peripheral compartment to the central compartment.

## Results

### Demographic and clinical data

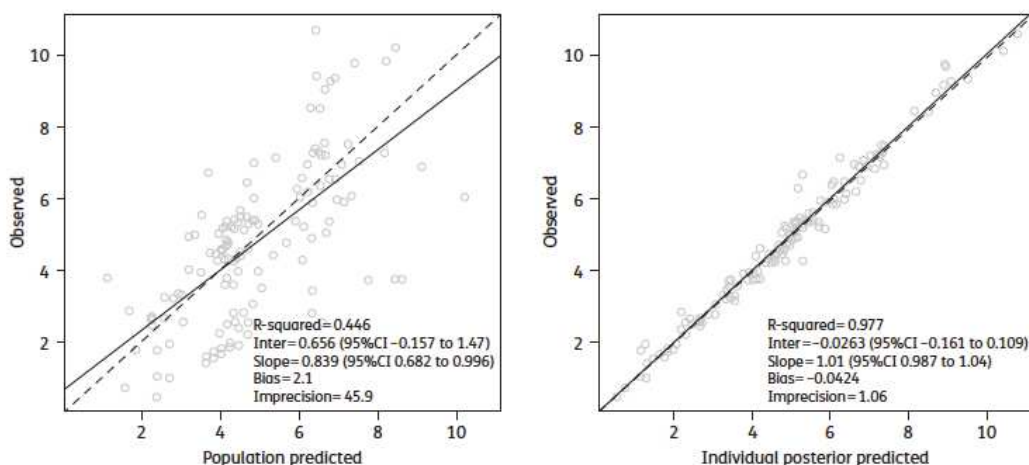
Eleven patients were recruited into the study per protocol. Demographic and clinical data are presented in Table 1. Nine of the 11 patients required vasopressor support. The causes of infection were pulmonary ( $n=3$ ), intra-abdominal ( $n=4$ ), urinary tract ( $n=2$ ) infections and septicæmia ( $n=2$ ). The microbiological samples were positive in 5 (45%) patients and identified two *K. pneumoniae*, two *E. coli*, one *Enterococcus faecium*, one *Enterococcus faecalis*, one *Enterobacter cloacae*, one *Moraxella catarrhalis* and two staphylococci. The range of Gram-negative bacilli MICs was 0.25–4 mg/L. Among the 11 included patients, 6 (55%) died.

### RRT

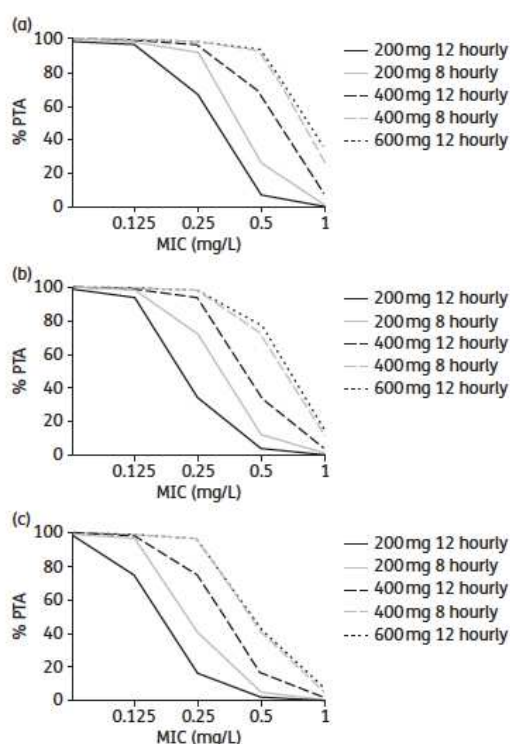
Six patients underwent both CVWHF and CVVHDF. Of the remaining patients, three received CVWHF and two CVVHDF only. The comparison of RRT settings across both CVWHF and CVVHDF treatments is shown in Table 2.

### Pharmacokinetic model building

The mean observed concentration–time profile of ciprofloxacin is shown in Figure 1. A two-compartment linear model best described the time-course of 141 total plasma concentrations of ciprofloxacin. This model included zero order input of drug into the central compartment. The only covariate that improved the fit of the model was, for ciprofloxacin clearance, total body weight normalized to 90 kg. The final model was described as



**Figure 2.** Diagnostic plots for the final covariate model. Observed versus population predicted concentrations (left-hand panel) and individual predicted concentrations (right-hand panel) in plasma. Data are presented in mg/L.



**Figure 3.** Monte Carlo simulations and PTA in plasma for various iv ciprofloxacin doses for body weights of (a) 50, (b) 90 and (c) 140 kg.

follows:

$$\text{Ciprofloxacin CL} = \text{TVCL} \times \frac{\text{total body weight}}{90}$$

where CL is clearance and TVCL is the typical value of clearance. The population pharmacokinetic parameter estimates from the final covariate model are shown in Table 3. After accounting for patient weight, mean CVVHF clearance was 11.8 (9.9) and mean CVVHDF clearance was 10.3 (7.4) L/h ( $P=0.43$ ). The diagnostic plots to confirm the goodness of fit of the model were considered acceptable and are shown in Figure 2. The final covariate model was then used for dosing simulations.

**Dosing simulations**

The Monte Carlo simulations and PTAs for various ciprofloxacin doses for patients that are 50, 90 or 140 kg are described in Figure 3. These simulations generally describe that the PTA is lower for patients with a higher total body weight with a reduced PTA for the same MIC. Increasing doses and/or frequency results in increased PTA.

**Fractional target attainment**

The fractional target attainments for the simulated PTAs for a range of ciprofloxacin doses, dose frequencies and patient body weights against susceptible MIC distributions ( $\text{MIC} \leq 1.0 \text{ mg/L}$ ) for *A. baumannii*, *K. pneumoniae*, *E. coli* and *P. aeruginosa* are shown in Table 4. These data show that for a body weight of 50 kg, 200 mg iv 12 hourly is sufficient for *K. pneumoniae* and *E. coli* whereas *A. baumannii* and *P. aeruginosa* require 400 mg iv 12 hourly. For body weights of 90 and 140 kg, 200 mg iv 12 hourly and 200 mg 8 hourly is required for *K. pneumoniae* and *E. coli*, respectively. Where susceptible *A. baumannii* and *P. aeruginosa* are present, 400 mg iv 8 hourly is required for a 90 kg patient and none of the simulated doses was sufficient for a 140 kg patient.

**Table 4.** Fractional target attainment for the various ciprofloxacin doses for patients with body weights of 50, 90 or 140 kg for an *A. baumannii*, *K. pneumoniae*, *E. coli* and *P. aeruginosa* MIC distribution

Body weight (kg)	iv dose/frequency	<i>A. baumannii</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
50	200 mg 12 hourly	65.8	90.3	96.5	70.1
	200 mg 8 hourly	78.1	93.2	97.9	78.9
	400 mg 12 hourly	86.7	95.5	98.6	86.2
	400 mg 8 hourly	93.3	97.6	99.3	92.5
	600 mg 12 hourly	94.0	97.8	95.0	93.2
90	200 mg 12 hourly	53.3	87.8	96.9	62.0
	200 mg 8 hourly	69.2	91.3	98.1	73.0
	400 mg 12 hourly	80.3	93.7	98.9	80.8
	400 mg 8 hourly	88.9	96.2	99.0	88.3
	600 mg 12 hourly	89.8	96.5	93.5	89.1
140	200 mg 12 hourly	40.7	84.6	93.5	50.3
	200 mg 8 hourly	56.8	88.8	95.5	64.9
	400 mg 12 hourly	70.9	91.7	97.1	74.2
	400 mg 8 hourly	82.8	94.4	98.4	82.8
	600 mg 12 hourly	83.0	94.4	98.4	83.1

Doses achieving the *a priori* target of PTA of  $\text{AUC/MIC} \geq 125$  against at least 85% of isolates are shaded grey.

## Discussion

The results of the present study suggest that high ciprofloxacin dosing regimens (400 mg iv 8 hourly) should be used in critically ill patients undergoing CRRT when difficult-to-treat pathogens are suspected and in high weight patients (>90 kg). Indeed, our pharmacokinetic/pharmacodynamic analysis showed that using ciprofloxacin dosing regimens of 400 mg 12 hourly or less could expose critically ill patients undergoing CRRT to underdosing when difficult-to-treat pathogens (e.g. *P. aeruginosa* or *A. baumannii*) are suspected.

Ciprofloxacin has been used for many years to treat nosocomial infections. However, the likelihood of multidrug bacterial resistance increases with fluoroquinolones when these drugs are used at inappropriate doses.<sup>22</sup> CRRT could particularly enhance the risk of underdosing by leading to drug extracorporeal clearance and could worsen life-threatening infection prognosis. The dosing regimen of 400 mg 8 hourly in the present study is most likely to achieve pharmacodynamic targets in patients of higher body weight and with suspected high MIC pathogens when weight-based RRT are used. Higher doses of ciprofloxacin have been previously reported as the required dosing regimen in patients with difficult-to-treat infections (in particular *P. aeruginosa* infections) but not receiving RRT.<sup>23,24</sup>

The present study did not show any influence of the CRRT mode on ciprofloxacin clearance, as CVVHF and CVVHDF clearances are similar when standardized settings and equal RRT doses are applied [11.8 (9.9) versus 10.3 (7.4) L/h, respectively,  $P=0.43$ ]. The influence of RRT settings on the pharmacokinetics of antibiotics has been previously described.<sup>6,25,26</sup> The extent of drug clearance is thought proportional to the membrane surface area and dependent on the mode of replacement fluid infusion (pre- or post-dilution mode) and on the ultrafiltration and/or dialysate flow rates applied.<sup>6</sup> Malone et al.<sup>13</sup> compared the pharmacokinetics of ciprofloxacin in 10 patients during CVVHDF ( $n=5$ ) and CVVHF ( $n=5$ ) using a 400 mg iv 12 or 24 hourly dosing regimen. They reported similar sieving coefficients (0.67 versus 0.63) and a 17% RRT clearance in both groups. However, the effluent rates were adjusted according to the renal consultant assessment and so, widely varied in each group. In our study, using similar weight-based effluent rates, post-dilution mode and similar membrane in both groups, we did not show any significant differences in ciprofloxacin RRT clearances. These data suggest that ciprofloxacin dosing regimens should not be adjusted to the mode of CRRT applied when the same weight-based RRT dose is prescribed. Higher dosing regimens should be used when high MICs pathogens are suspected or in high weight patients whatever the RRT mode. As we used mL/kg/h dosing of RRT, higher weight patients had higher effluent rates and so, higher drug clearance. However, this effect is adequately described by weight in the present model. The only RRT setting that statistically differs between the two groups was the fraction ratio (ultrafiltration flow rate/blood flow rate) [12% (8%–14%) in the CVVHDF group versus 19% (15%–20%) in the CVVHF group,  $P=0.009$ ]. This ratio reflects the haemoconcentration across the filter and it is classically recommended to maintain it above 25% in the post-dilution technique.<sup>27</sup> This parameter does not seem to influence ciprofloxacin RRT clearance in the present study.

Regarding parameter estimates from our population pharmacokinetic model, the total ciprofloxacin clearance reported in the

present study ( $10.7 \pm 5.3$  L/h) was close to the total clearance reported by Wallis et al.<sup>14</sup> ( $12.2 \pm 4.3$  L/h) and slightly higher to those reported by Spooner et al.<sup>15</sup> ( $8.6 \pm 2.7$  L/h). Wallis et al.<sup>14</sup> reported that a 3 L/h effluent rate of CVVHDF resulted in only 21% of total ciprofloxacin clearance being due to RRT. Spooner et al.<sup>15</sup> found that a 3.5 L/h effluent flow rate was responsible for removing 26% of ciprofloxacin during CVVHDF. As we used a lower effluent flow rate (an average of 2.5 L/h), the amount of ciprofloxacin removed during RRT should be slightly inferior in the present study.

Similarly to previous studies,<sup>9–11</sup> we reported profound variability in ciprofloxacin pharmacokinetics in critically ill patients regardless of the RRT mode. Ciprofloxacin exhibits multiple routes of clearance. In healthy volunteers, 50%–60% of ciprofloxacin is eliminated by the renal route and 20% by the hepatic route.<sup>28</sup> In AKI, significant transintestinal excretion may occur as a protective pathway limiting drug accumulation. These changes in elimination routes as well as hypoalbuminaemia and increased volume of distribution could explain the high variability in pharmacokinetic parameters in critically ill patients undergoing RRT.<sup>4,28</sup> This wide variability in ciprofloxacin plasma levels highlights that TDM should be routinely used in the ICUs to optimize antibiotic therapy in critically ill patients.

This study has limitations we would like to declare. First, the size of the sample is small, although it is the largest study that reported data of ciprofloxacin pharmacokinetics during RRT. Second, we could not assess mechanistically if the sub-therapeutic concentrations observed were caused by RRT or non-RRT clearance because the disposition of ciprofloxacin into RRT effluent was not described in this study, although this limitation does not alter the end result of our dosing recommendations. In addition, the effect of the residual renal function on total body clearance could not be assessed in the present study and we did not report pharmacokinetics data when CRRT is off. Third, liver dysfunction or impairment was not specifically assessed and this may have helped characterize the extent of transintestinal clearance of ciprofloxacin. However, none of the studied patients presented hepatic failure according to the SOFA hepatic score. Fourth, this study was not designed to measure any difference in patient outcome, such as clinical cure or survival.

## Conclusions

The present study highlights the high pharmacokinetic variability of ciprofloxacin during CVVHF and CVVHDF. These results suggest that TDM would be the best option to optimize ciprofloxacin dosing regimens in critically ill patients undergoing CVVHF or CVVHDF. If TDM is not routinely available, high ciprofloxacin dosing regimens (400 mg 8 hourly) should be used. Sub-optimal achievement of therapeutic targets occurs at the EUCAST breakpoint MIC of 0.5–1.0 mg/L using current doses. Based on patient weight, higher ciprofloxacin dosing regimens should be used in critically ill patients undergoing CRRT regardless of the modality, particularly when difficult-to-treat pathogens are suspected.

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### Transparency declarations

None to declare.

### Author contributions

C. R. made substantial contributions to conception, study design, acquisition and interpretation of data and drafting the manuscript and approved the final version to be published. S. C. W. made substantial contributions to acquisition, analysis and interpretation of data and revising the manuscript for important intellectual content and approved the final version to be published. B. L. made substantial contributions to acquisition, analysis and interpretation of data and revising the manuscript for important intellectual content and approved the final version to be published. J.-Y. L. made substantial contributions to conception, study design, interpretation of data and drafting the manuscript and approved the final version to be published. J. L. made substantial contributions to conception, study design, interpretation of data and revising the manuscript for important intellectual content and approved the final version to be published. L. M. made substantial contributions to conception, study design, interpretation of data and drafting the manuscript and approved the final version to be published. J. A. R. made substantial contributions to conception, study design, analysis and interpretation of data, drafting the manuscript and revising the manuscript for important intellectual content and approved the final version to be published.

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L'ensemble de ces travaux portant sur l'analyse PK de population de différents antibiotiques dans le contexte de sepsis et d'EERc corrobore les résultats de l'étude DALI, première étude à souligner le risque de posologies inappropriées chez les patients de réanimation.<sup>9</sup> Ces travaux nous ont amené à nous poser la question de l'impact potentiel de l'EER et du sepsis pour d'autres classes d'anti-infectieux et notamment pour les antifongiques. Le risque de sous- ou de surdosage dans la population de réanimation pourrait conduire à des échecs thérapeutiques. Dans la faible cohorte de l'étude DALI, 33% des patients présentaient des concentrations plasmatiques d'antifongiques en dessous des cibles thérapeutiques.<sup>94</sup> Nous avons donc évalué, dans un travail prospectif sur 9 patients sous EERc, l'influence du sepsis sur un antifongique appartenant à la classe des échinocandines : la caspofungine à l'aide d'une analyse PK de population.

**Article 6 : Analyse PK de population de la caspofungine dans une population de patients septiques sous CVVH vs CVVHDF. *Clin Pharmacokinet*, rang A, impact factor 2016 : 5,21.<sup>95</sup>**

Les infections fongiques restent associées à une mortalité élevée.<sup>96</sup> Les échinocandines font partie du traitement antifongique empirique de première intention dans le choc septique lorsqu'une levure est suspectée.<sup>97,98</sup> Les propriétés physico-chimiques de cette classe d'antibiotique sont marquées par un caractère lipophile leur conférant un volume de distribution élevé ainsi qu'une bonne diffusion tissulaire, une élimination principalement par métabolisation hépatique et une forte liaison protéique (95%). Leur activité est concentration-dépendante associée à un effet post antifongique prolongé. Dans le contexte de sepsis, la survenue d'une hypoalbuminémie majeure et de défaillance d'organes pourrait altérer la PK de ces antifongiques. De plus, ces molécules présentent la particularité d'adhérer aux surfaces inertes et d'agir sur le biofilm. Lorsqu'une EER est appliquée, une partie de ces molécules

pourrait être adsorbée sur la membrane de dialyse. La dose habituelle recommandée de caspofungine est de 70 mg en dose de charge suivie d'une dose d'entretien de 50 mg journalier.<sup>99</sup> De précédentes études ont rapporté des données contradictoires quant à l'influence du sepsis, la nécessité d'adaptation des posologies et la variabilité inter-individuelle des concentrations plasmatiques observée dans la population de patients de réanimation.<sup>71,100</sup>

Dans ce travail, les 12 profils PK obtenus ont permis de développer un modèle PK pop pour cette population de patients septiques épurés par CVVH ou CVVHDF. Un modèle bi-compartimental incluant le poids réel comme covariable corrélée à la clairance totale de la caspofungine ainsi qu'au Vd a été retenu comme modèle final. Dans la littérature, la covariable poids est inconstamment retrouvée comme affectant la PK de la caspofungine.<sup>101</sup> L'analyse mécanistique de la quantité de caspofungine épurée et/ou adsorbée par l'EER montre que cette quantité est négligeable quelque soit la technique d'EER appliquée (clairance totale :  $0.048 \pm 0.12$  L/h dans le groupe CVVH,  $0.042 \pm 0.042$  L/h dans le groupe CVVHDF). De façon plus intéressante, lorsque l'on considère les résultats des MCS prenant en compte les cibles PK/PD d'AUC/CMI associées à une diminution du compte bactérien de 1 log<sub>10</sub> à 24h *in vivo* et définies selon l'espèce de Candida considéré, seuls les schémas posologiques comprenant une augmentation de la dose de charge à 100 mg permettaient d'atteindre ces cibles. Les doses recommandées par les MCS pour la population de patients de réanimation en choc septique et sous EERc sont :

- une dose de charge de 100 mg suivie d'une dose d'entretien de 50 mg pour les patients avec un poids réel < 80 kg
- une dose de charge de 100 mg suivie d'une dose d'entretien de 70 mg pour les patients avec un poids réel  $\geq$  80 kg

Pour les espèces de *Candida* présentant une CMI  $>0.006$  mg/L, aucun des schémas posologiques testés ne permettaient d'atteindre les cibles d'AUC/CMI quelque soit l'espèce de *Candida* considérée.

La principale limite de cette étude réside en l'absence de mesures des concentrations libres en caspofungine. Bien que plus pertinentes pour les molécules fortement liées aux protéines, ces concentrations sont extrêmement difficiles à obtenir du fait des contraintes techniques qu'elles engendrent et notamment la nécessité de recourir à une HPLC/spectrométrie de masse très sensible.

**Conclusion : Ce travail met en évidence le risque de sous dosage plasmatique en caspofungine lorsque les doses conventionnelles recommandées sont prescrites et confirme la grande variabilité inter-individuelle des concentrations observées dans la population de patients en choc septique sous EERc. Les résultats de cette analyse PK de population encourage à utiliser des doses de charge plus élevées du fait de l'augmentation de Vd rencontrée dans cette population.**

Article 6 : Analyse PK de population de la caspofungine dans une population de patients septiques sous CVVH vs CVVHDF. *Clin Pharmacokinet*, rang A, impact factor 2016 : 5,21.<sup>95</sup>

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ORIGINAL RESEARCH ARTICLE

## Caspofungin Population Pharmacokinetics in Critically Ill Patients Undergoing Continuous Veno-Venous Haemofiltration or Haemodiafiltration

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### Abstract

**Background and Objective** Sepsis and continuous renal replacement therapy (CRRT) can both significantly affect antifungal pharmacokinetics. This study aimed to describe the pharmacokinetics of caspofungin in critically ill patients during different CRRT modes.

**Methods** Patients receiving caspofungin and undergoing continuous veno-venous haemofiltration (CVVH) or haemodiafiltration (CVVHDF) were eligible to take part in the study. Blood samples were collected at seven sampling times during a dosing interval. Demographics and clinical data were recorded. Population pharmacokinetic analysis

and Monte-Carlo simulation were undertaken using Pmetrics.

**Results** Twelve pharmacokinetic profiles from nine patients were analysed. The caspofungin CRRT clearance (CL) was  $0.048 \pm 0.12$  L/h for CVVH and  $0.042 \pm 0.042$  L/h for CVVHDF. A two-compartment linear model best described the data. Patient weight was the only covariate affecting drug CL and central volume. The mean (standard deviation) parameter estimates were  $0.64 \pm 0.12$  L/h for CL,  $9.35 \pm 3.56$  L for central volume,  $0.25 \pm 0.19$  per h for the rate constant for drug distribution from central to peripheral compartments and  $0.19 \pm 0.10$  per h from peripheral to central compartments. Based on simulation results, a caspofungin 100 mg loading dose followed by a 50 mg maintenance dose for patients with a total body weight of  $\leq 80$  kg best achieved the pharmacokinetic/PD targets whilst a 70 mg maintenance dose was required for patients with a weight of  $>80$  kg.

**Conclusion** No caspofungin dosing adjustment is necessary for patients undergoing either form of CRRT. However, higher than recommended loading doses of caspofungin are required to achieve pharmacokinetic/pharmacodynamic targets in critically ill patients.

Registration: ClinicalTrials.gov Identifier NCT01403220

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### Key Points

The caspofungin clearance related to continuous veno-venous haemofiltration or haemodiafiltration is negligible.

Higher than recommended loading doses (i.e. 100 mg) are required to achieve optimal caspofungin exposure in critically ill patients.

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## 1 Introduction

Invasive fungal infections, largely due to *Candida* spp., are a major cause of morbidity and mortality among intensive care unit (ICU) patients [1]. Early initiation of adequate antifungal therapy is crucial to improve patients' prognosis [2–4]. Echinocandins are commonly used antifungal agents that exhibit a concentration-dependent broad-spectrum fungicidal activity with prolonged post-antifungal effects. In critically ill patients, patho-physiological changes such as hepatic and/or renal dysfunctions, organ support, hypo-albuminaemia or increased capillary permeability can alter antimicrobial clearance (CL) and volume of distribution ( $V_d$ ) [5]. Continuous renal replacement therapy (CRRT) is often applied in haemodynamically unstable critically ill patients with acute kidney injury (AKI) [6]. The CRRT practices may differ between ICUs; however, continuous veno-venous haemofiltration (CVVH) and continuous veno-venous haemodiafiltration (CVVHDF) are the most widely used modes [7]. The CRRT settings, type of haemofilter or the fluid replacement mode (pre- or post-dilution) applied may alter antimicrobial pharmacokinetics by removing or adsorbing drug at a different magnitude [8–10]. Due to their high protein binding (94–99%), the presence of hypo-albuminaemia that commonly occurs in ICU patients and their potential adherence to synthetic surfaces, the pharmacokinetics of echinocandins can be affected in critically ill patients receiving CRRT [11]. A moderate to high inter-individual caspofungin variability has been reported in ICU patients [12–15]. For example, Sinnollareddy et al. [15] found a large inter-individual variability for anidulafungin and caspofungin in critically ill patients without CRRT. Conversely, previous studies including ICU patients on CRRT reported moderate inter-individual variability for micafungin (coefficient of variation [CV] 57.9%, 95% confidence interval [CI] 57.7–58.2) and caspofungin (CV 45.6%, 95% CI 41.3–53) [12, 13]. In the context of renal impairment, no dosing adjustment is recommended as caspofungin has very low (1–2%) renal CL [16, 17]. Nevertheless, increased caspofungin exposure in patients with renal impairment has been observed after the first dose [16]. As a result, optimal dosing may be highly challenging for clinicians in the context of critical illness and CRRT and caspofungin dosing adjustment may be necessary to ensure adequate antifungal exposure. However, data focusing on ICU patients receiving CRRT are limited [18].

The aims of this study were to determine whether different CRRT modes may affect caspofungin pharmacokinetics and to describe the population pharmacokinetics of caspofungin in critically ill patients receiving CVVHDF or CVVH. We then sought to perform Monte-Carlo

simulations to determine optimised dosing regimens for achieving pharmacokinetic/pharmacodynamic targets.

## 2 Materials and Methods

### 2.1 Setting

This observational pharmacokinetic study was a sub-study of a randomised trial comparing the efficacy of equal dose of CVVH (30 mL/kg/h ultrafiltrate flow rate) and CVVHDF (15 mL/kg/h dialysate flow rate + 15 mL/kg/h ultrafiltrate flow rate) in a tertiary referral ICU (ClinicalTrials.gov NCT01403220, completed but as yet unpublished) [10]. Ethics approval was obtained from the local ethics committee of Nîmes (Comité de Protection des Personnes Sud Méditerranée III 2012.02.05). Written informed consent was obtained from either the patient or their nominated substitute decision maker.

### 2.2 Study Population

Patient eligibility criteria for this study were:

- AKI necessitating either CVVH or CVVHDF according to the randomly allocated mode in the primary study and
- Clinical indication for caspofungin.

Patients were randomised to CVVH or CVVHDF (according to the primary study protocol) when the need for CRRT was first identified. The protocol of the primary study required that the patient then received the alternative CRRT mode for the subsequent CRRT session. When the patient was taking antibiotic therapy across both CRRT modes, they were sampled on two different occasions encompassing both CVVH and CVVHDF.

Patients were excluded patients if they had a:

- Requirement of CRRT for cardiogenic pulmonary oedema, metabolic acidosis (pH <7.15,  $\text{HCO}_3^-$  < 12 mmol/L) or hyperkalaemia >6.5 mmol/L; or
- History of allergy or contraindication to caspofungin.

### 2.3 Continuous Renal Replacement Therapy (CRRT) Settings

Both techniques were performed using an Aquarius™ system (Nikkiso, Tokyo, Japan) and a polysulfone-type haemofilter with a surface area of 1.9 m<sup>2</sup> (Aquamax HF19; Edwards Lifesciences, St Prex, Switzerland).

The CRRT settings were as follows:

- A 30 mL/kg/h ultrafiltrate rate for CVVHF and a 15 mL/kg/h ultrafiltrate rate + 15 mL/kg/h dialysate flow rate for CVVHDF. For both techniques, fluid replacement was applied post-dilution.
- The net removal fluid rate was set at the physician's discretion between 0 and 200 mL/h.
- The targeted blood flow rate was aimed at providing a filtration ratio <20%. The filtration ratio was calculated as follows: (ultrafiltrate flow rate + net fluid removal)/blood flow rate. It is the fraction of plasma that is removed from blood during haemofiltration [19].

## 2.4 Study Protocol

A dosing regimen of a caspofungin 70 mg loading dose and a 50 mg maintenance dose for patients with a total body weight ≤80 kg or a 70 mg maintenance dose for patients with a total body weight >80 kg was administered intravenously over 1 h as part of the patients' prescribed antimicrobial therapy. Between day 1 and day 4 of anti-fungal therapy, a pharmacokinetic curve of five to seven blood samples over a 24-h period was drawn. Blood samples from the CRRT circuit before the haemofilter (pre-filter samples) to determine total plasma caspofungin concentrations were taken at baseline (pre-dose) and 1, 2, 4, 8, 12 and 24 h after the start of caspofungin infusion. Blood samples immediately after the haemofilter (post-filter samples) were taken at 2, 4, 8, 12 and 24 h after the start of caspofungin infusion.

The CL of caspofungin by CRRT was assessed as follows:

$$\text{Caspofungin CL by CRRT} = \frac{(C_{\text{pre}} - C_{\text{cor,post}}) / C_{\text{cor,post}}}{\times \text{BFR}}$$

where  $C_{\text{pre}}$  is the caspofungin pre-haemofilter concentration,  $C_{\text{cor,post}}$  is the corrected caspofungin post-haemofilter concentration and BFR is the CRRT machine blood flow rate.

Post-haemofilter concentrations were corrected post-dilution as follows:

$$C_{\text{cor,post}} = C_{\text{post}} \times (\text{BFR} - \text{PDR} - \text{FRR}) / \text{BFR}$$

where  $C_{\text{post}}$  is the measured caspofungin post-haemofilter concentration, BFR is the blood flow rate, PDR is the post-dilution rate and FRR is the fluid removal rate.

## 2.5 Sample Handling and Storage

Blood samples were immediately placed on ice and centrifuged at 3000 rpm for 10 min then stored at -80 °C. Samples were transported (with a temperature log on dry ice)

by a commercial courier company to the Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Queensland, Australia, for further analysis.

## 2.6 Drug Assay

Total caspofungin concentrations in plasma were measured by a validated ultra-high pressure liquid chromatography (UHPLC)-tandem mass spectrometry (UHPLC-MS/MS) method, from 0.1 to 20 mg/L on a Shimadzu Nexera UHPLC coupled to a Shimadzu 8030 + triple quadrupole mass spectrometer (Shimadzu, Kyoto, Japan). Clinical samples were assayed alongside calibrators and quality controls and met batch acceptance criteria of the US Food and Drug Administration's guidance for industry on bio-analysis (available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf>). The assay method was validated for linearity, lower limit of quantification, matrix effects, precision and accuracy, and stock stability. Intra-batch precision was ≤3.3% and accuracy was ≤11.0% at the three concentrations tested (0.6, 3 and 18 µg/mL). Inter-batch precision was ≤6.1% and accuracy was ≤1.8% at the three concentrations tested.

## 2.7 Patient Data Collection

The following clinical and demographic data were collected: age, weight, height, sex, co-morbidities, Simplified Acute Physiology Score II (SAPS II) [20] at ICU admission, modified Sequential Organ Failure Assessment (SOFA) [21] score at ICU admission and on sampling day, 12-h urine output and mean arterial pressure (MAP) and 28-day outcome. During the CRRT treatment, CVVHF or CVVHDF settings were also recorded: blood flow rate, ultrafiltration flow rate, dialysate flow rate, filtration fraction, fluid removal rate and transmembrane pressure. Data on the type of infection, microbiological cultures and E-test minimal inhibitory concentration (MIC) (BioMérieux, Marcy-l'Étoile, France) (if available) were also collected.

## 2.8 Population Pharmacokinetic Modelling

To describe total caspofungin disposition, one- and two-compartment pharmacokinetic models were developed with the Non-Parametric Adaptive Grid (NPAG) algorithm within the freely available Pmetrics software package for R (Los Angeles, CA, USA) [22, 23]. We used the NPAG algorithm as it creates a non-parametric population model consisting of discrete support points, each with a set of estimates for all parameters in the model plus an associated probability (weight) of that set of estimates. There is no need for any assumption about the underlying distribution



of model parameter values. CL from the central compartment and intercompartmental distribution (two-compartment model) into the peripheral compartment were modelled as first-order processes. Discrimination between different models used comparison of the  $-2$  log-likelihood ( $-2LL$ ) values. A  $p$  value of  $<0.05$  was considered statistically significant.

### 2.9 Population Pharmacokinetics Covariate Screening

Age, sex, body weight, SOFA, serum creatinine concentration, serum albumin concentration, residual urine output, CRRT modality (CVVH or CVVHDF), blood flow rate, ultrafiltration rate and fluid removal were evaluated as clinically relevant and physiologically plausible covariates. Screening and selection of covariates was performed using a stepwise multivariate linear regression analysis to explore the potential relationship between covariates and Bayesian individual posterior pharmacokinetic parameters. The covariates that were significantly associated with pharmacokinetic parameters were entered separately into the structural model. The influence of the covariate on each pharmacokinetic parameter was tested using a linear or allometric function. If inclusion of the covariate resulted in a statistically significant improvement in the log-likelihood (LL) values ( $p < 0.05$ ) and/or improved the goodness-of-fit plots or decreased between subject variability, then the covariate was retained in the final model.

### 2.10 Model Diagnostics

Goodness of fit was assessed by linear regression, with an observed–predicted plot, coefficients of determination and LL values. Predictive performance evaluation was based on the mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models. The internal validity of the population pharmacokinetic model was assessed using the bootstrap resampling method ( $n = 1000$ ) and normalised prediction distribution errors (NPDEs) [24]. Using the visual predictive check (VPC) method, simulated observations distribution obtained from the final model were plotted with the observed concentrations as a function of time. NPDE plots were checked for normal distribution characteristics and trends in the data errors.

### 2.11 Probability of Target Attainment

Given the lack of well-established clinical pharmacokinetic/pharmacodynamic targets and breakpoints, preclinical pharmacokinetic/pharmacodynamic targets associated with a  $1 \log_{10}$  kill/24 h were used for the Monte-Carlo

simulations (area under the plasma concentration–time curve from time zero to 24 h [ $AUC_{24}/MIC >865$  for *Candida albicans* and  $AUC_{24}/MIC >450$  for *C. glabrata* [25]).

Monte-Carlo simulations ( $n = 1000$ ) were employed using Pmetrics to determine the probability of target attainment (PTA) of achieving the preclinical pharmacokinetic/pharmacodynamic targets of  $AUC_{24}/MIC \geq 865$  for *C. albicans* and  $AUC_{24}/MIC \geq 450$  for *C. glabrata* [25] for varying MICs (0.008–4 mg/L) (Clinical Laboratory Standards Institute [CLSI] method) after administration of a loading dose (0–24 h) and again at assumed pharmacokinetic steady state of 96–120 h. Intravenous loading doses of caspofungin 70, 100, 150 or 200 mg were tested. The simulated maintenance doses were 50, 70 or 100 mg after administration of an intravenous loading dose of caspofungin 100 mg. Three different total body weights (60, 80 and 100 kg) were tested, which reflected the broad distribution of values observed in this patient population.

### 2.12 Fractional Target Attainment

The MIC data used to determine fractional target attainment for *C. albicans* and *C. glabrata* were obtained from Pfaller et al. [26]. The fractional target attainment identifies the likely success of treatment by comparing the pharmacodynamic exposure (PTA) against an MIC distribution (CLSI method). A caspofungin dosing regimen was considered successful if the FTA value was  $\geq 90\%$ .

### 2.13 Statistical Analysis

Continuous data are presented as the mean (standard deviation [SD]) or median [interquartile range] and categorical data are presented as counts (%). Correlation was assessed by means of a scatter graph and Pearson correlation coefficient ( $r$ ). A  $p$  value  $<0.05$  was considered as statistical significance, and all analyses were performed using GraphPad PRISM software 6.0 (GraphPad Software, San Diego, CA, USA).

## 3 Results

### 3.1 Demographic and Clinical Data

Nine patients were recruited in the study per protocol analysis contributing to 12 pharmacokinetic profiles analysed. Demographic and clinical data from the studied population are shown in Table 1. All patients required vasopressor support during the studied renal replacement therapy (RRT) sessions. The causes of septic shock were peritonitis ( $n = 6$ ), catheter-related infection ( $n = 1$ ),

**Table 1** Demographic data for the studied population ( $n = 9$ )

Demographics	$n$ or median [IQR]
Sex: female/male	2/7
Age (years)	62 [52–72]
Weight (kg) at admission	84 [75–93]
Height (cm)	170 [163–180]
Body Mass Index ( $\text{kg}/\text{m}^2$ )	27 [25.7–31.1]
Co-morbidities	
Hypertension	4
Chronic heart failure	0
COPD	4
Child Pugh B cirrhosis	2
Severity scores	
SAPS II at admission	55 [49–60]
SOFA at admission	11 [9–13]

*COPD* chronic obstructive pulmonary disease, *IQR* interquartile range, *SAPS II Simplified Acute Physiology Score II*, *SOFA* Sequential Organ Failure Assessment score

mediastinitis ( $n = 1$ ) and unknown ( $n = 1$ ). The microbiological samples identified fungi in six (67%) patients: *C. albicans* ( $n = 3$ ), *C. parapsilosis* ( $n = 2$ ), *C. tropicalis* ( $n = 1$ ) and *C. krusei* ( $n = 1$ ). The range of *Candida* MICs varied from 0.032 to 1.5 mg/L. The clinical response was unfavourable in four patients, and the 28-day mortality rate was 44.4%.

### 3.2 CRRT

Comparison of the CRRT settings across both CVVH and CVVHDF treatments are shown in Table 2. Caspofungin CRRT CL assessed from the pre- and post-haemofilter concentrations were  $0.048 \pm 0.12$  L/h for CVVH and  $0.042 \pm 0.042$  L/h for CVVHDF.

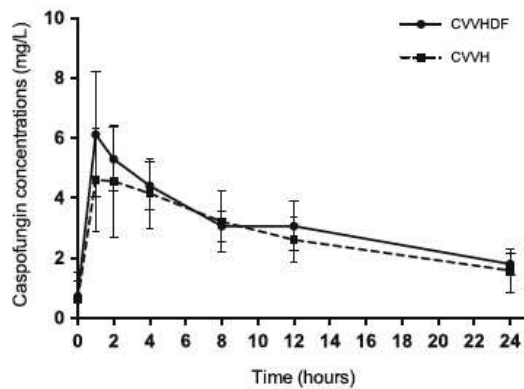
### 3.3 Pharmacokinetic Model

The mean observed concentration–time profile of 130 total caspofungin plasma concentrations is shown in Fig. 1. A two-compartment linear model best described the caspofungin plasma concentrations. This model included zero-order input of drug into the central compartment. After selection of the covariates, total body weight normalised to the mean population value (to the power of 0.75) was the only covariate that improved the fit of the model. After including total body weight on total caspofungin CL, the  $-2LL$  values decreased ( $-12$  change in  $-2LL$  [ $\Delta-2LL$ ]) but the difference was not statistically significant ( $p = 0.44$ ). Total body weight was then tested for its correlation with caspofungin central volume ( $-13 \Delta-2LL$ ,  $p = 0.44$ ). Based on biological plausibility, bias, imprecision and goodness-of-fit comparison between the structural

**Table 2** Clinical and biological data and continuous renal replacement therapy parameters during studied sessions

	Continuous renal replacement therapy parameters												
	Clinical and biological data					Continuous renal replacement therapy parameters							
	SOFA on sampling day	12-h urine output (mL)	MAP (mmHg)	Albumin (g/L)	Creatinine ( $\mu\text{mol}/\text{L}$ )	Urea (mmol/L)	HRT (h)	Blood flow rate (mL/min)	Dialysate flow rate (mL/kg/h)	Ultrafiltration rate (mL/kg/h)	Friction filtration ratio (%)	Trans-membrane pressure (mmHg)	Fluid removal (mL/kg/h)
CVVHDF ( $n = 7$ )	11 (8.5–15)	155 (84–340)	73 (67–77)	27.1 (26.2–29.3)	167 (156–200)	17 (14–23)	5.33 (4–10)	200 (180–200)	14.9 (14.3–15.4)	15 (14.6–15.6)	11 (10–12)	46 (32–51)	50 (10–70)
CVVH ( $n = 5$ )	13 (12–13)	200 (0–200)	83 (58–86)	22.8 (21.4–26.3)	144 (130–147)	11.2 (9–11.7)	4 (1–10)	200 (190–200)	NA	30 (28.6–30.6)	20 (19–21)	87 (80–120)	100 (50–100)

Data are expressed as median (1st–3rd interquartile)  
 CVVHDF continuous veno-venous haemofiltration, CVVHDF continuous veno-venous haemodiafiltration, HRT haemofilter running time (time between start of the CRRT session and start of pharmacokinetic sampling), IQR interquartile range, MAP mean arterial pressure, NA not available, SOFA sequential organ failure assessment score



**Fig. 1** The observed mean concentration–time profiles for the dosing interval of caspofungin sampling in critically ill patients receiving continuous veno-venous haemofiltration (CVVH) ( $n = 5$ ) or continuous veno-venous haemodiafiltration (CVVHDF) ( $n = 7$ ). Error bars represent standard deviation

model and the two-compartment model allometrically scaled for CL and volume of the central compartment ( $V_c$ ), total body weight was retained in the final covariate model (Table 3). Including the CRRT mode in the model did not

improve the goodness of fit of the model. Therefore, the CRRT mode was not retained in the final model.

The final covariate model was described as follows:

$$\text{Caspofungin CL} = \text{TVCL} \times (\text{WT}/80)$$

$$\text{Caspofungin central volume} = \text{TVVc} \times (\text{WT}/80)^{0.75}$$

where TVCL is the typical value of total caspofungin CL, TVVc is the typical value of caspofungin central volume and WT is total body weight.

The mean (SD) population pharmacokinetic parameter estimates from the final covariate model are shown in Table 4. The diagnostic plots and the VPC to confirm the goodness of fit of the model were considered to be acceptable and are shown in Fig. 2. Figure 2 provides evidence that the model developed is appropriate to describe the time course of caspofungin plasma concentrations from the present patient group. Additionally, we numerically checked the proportion of observed concentrations below each quantile and we also checked with a binomial test the probability that the proportion differ from the expected by chance. Of the observed concentrations, 4.7% are below the 5th percentile of simulated concentrations ( $p = 1.00$ ), 50% below are the median ( $p = 1.00$ )

**Table 3** Comparison of candidate models after 100 cycles

Model	Parameters	-2LL	AIC	Bias	Imprecision
Structural model <sup>a</sup>	CL, $V_c$ , $k_{cp}$ , $k_{pc}$	109.93	120.9	-0.005	0.38
Final model <sup>b</sup>	Structural + allometric	96.49	107.5	0.002	0.19

Bias (mean weighted prediction error) and imprecision (bias-adjusted mean weighted squared prediction error) are calculated based on the median population parameter values for each model

-2LL -2log-likelihood, AIC Akaike Information Criteria, CL total caspofungin clearance,  $k_{cp}$  rate constant for drug distribution from the central to peripheral compartment,  $k_{pc}$  rate constant for drug distribution from the peripheral to central compartment,  $V_c$  volume of the central compartment

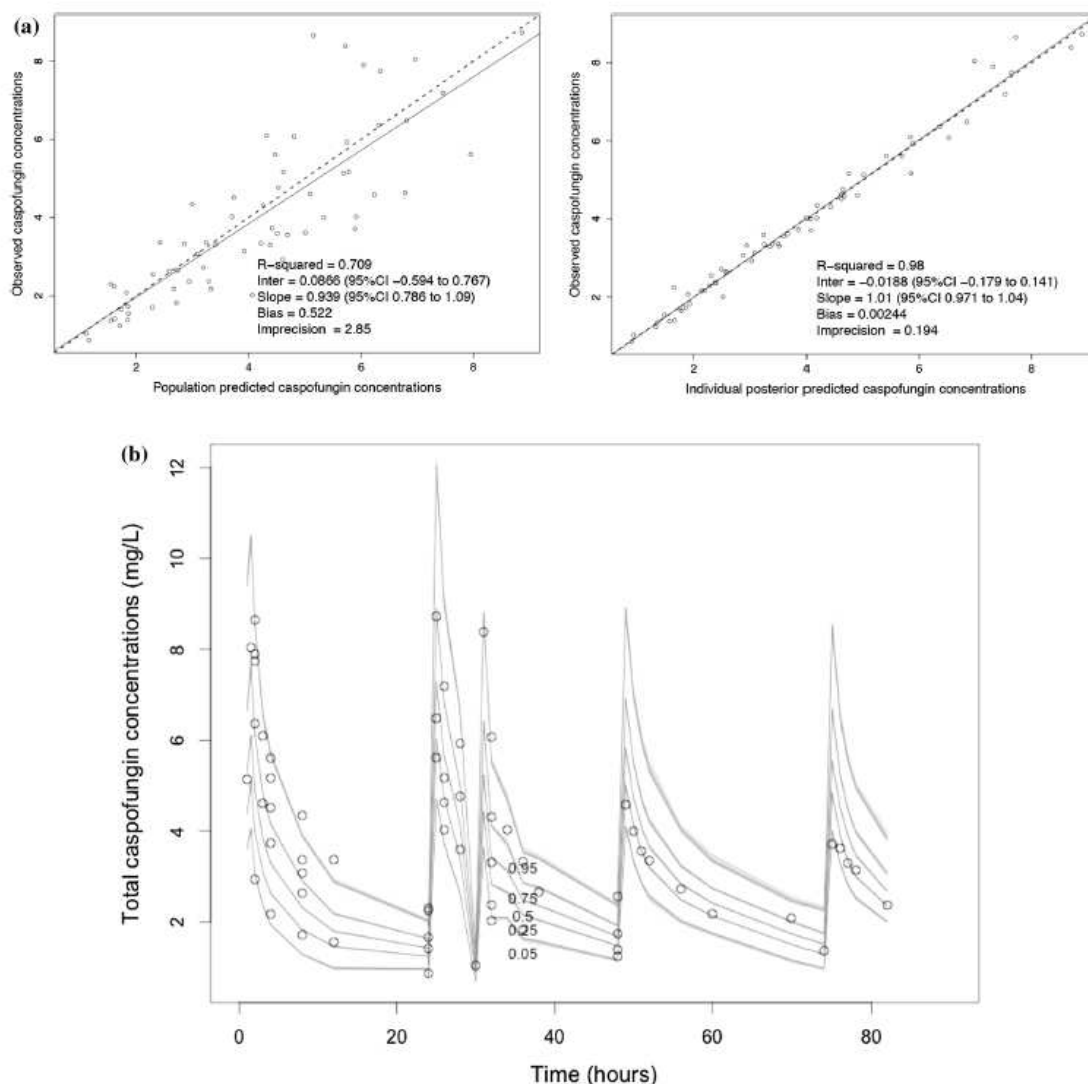
<sup>a</sup> Structural model is the two-compartment model without any covariates

<sup>b</sup> Final model is the two-compartment model with allometric scaling of model parameter values for total body weight

**Table 4** Parameter estimates for caspofungin from the final covariate two-compartment population pharmacokinetic model

Parameter estimates	Mean	Standard deviation	Coefficient of variation	Variance	Median	Bootstrap analysis	
						Median (95% CI)	MAWD (95% CI)
CL (L/h)	0.64	0.12	19.02	0.02	0.64	0.64 (0.56–0.77)	0.07 (0.00–0.16)
$V_c$ (L)	9.35	3.56	38.05	12.66	8.95	8.95 (5.02–12.83)	2.48 (0.00–4.09)
$k_{cp}$ (/h)	0.25	0.19	76.22	0.04	0.17	0.16 (0.16–0.22)	0.02 (0.00–0.12)
$k_{pc}$ (/h)	0.19	0.10	54.65	0.01	0.20	0.20 (0.10–0.23)	0.05 (0.00–0.13)

CI confidence interval, CL total caspofungin clearance,  $k_{cp}$  rate constant for drug distribution from the central to peripheral compartment,  $k_{pc}$  rate constant for drug distribution from the peripheral to central compartment, MAWD median absolute weighted deviation,  $V_c$  volume of the central compartment



**Fig. 2** Diagnostic plots for the final covariate two-compartment model: observed versus population predicted concentrations (*left panel*) and individual predicted concentrations (*right panel*) in plasma (*a*); and visual predictive check (*b*). The median and 5th-95th

percentiles, with 95% confidence intervals (CIs) (*light grey field*), based on simulations are shown. *Individual points* represent observed data

and 90.6% are below the 95th percentile ( $p = 0.14$ ). The final covariate model was then used for dosing simulations.

### 3.4 Dosing Simulations

The Monte-Carlo simulations and PTAs of  $AUC_{24}/MIC \geq 865$  for *C. albicans* and  $AUC_{24}/MIC \geq 450$  for *C. glabrata* [25] for various intravenous caspofungin doses for patients with a total body weight of 60, 80 and 100 kg are

described in Figs. 3 and 4. These simulations showed that increasing loading doses resulted in increased PTA from 0 to 24 h of therapy.

### 3.5 Fractional Target Attainment

The fractional target attainments for the simulated PTAs for a range of caspofungin loading and maintenance doses and different patient body weights against an MIC

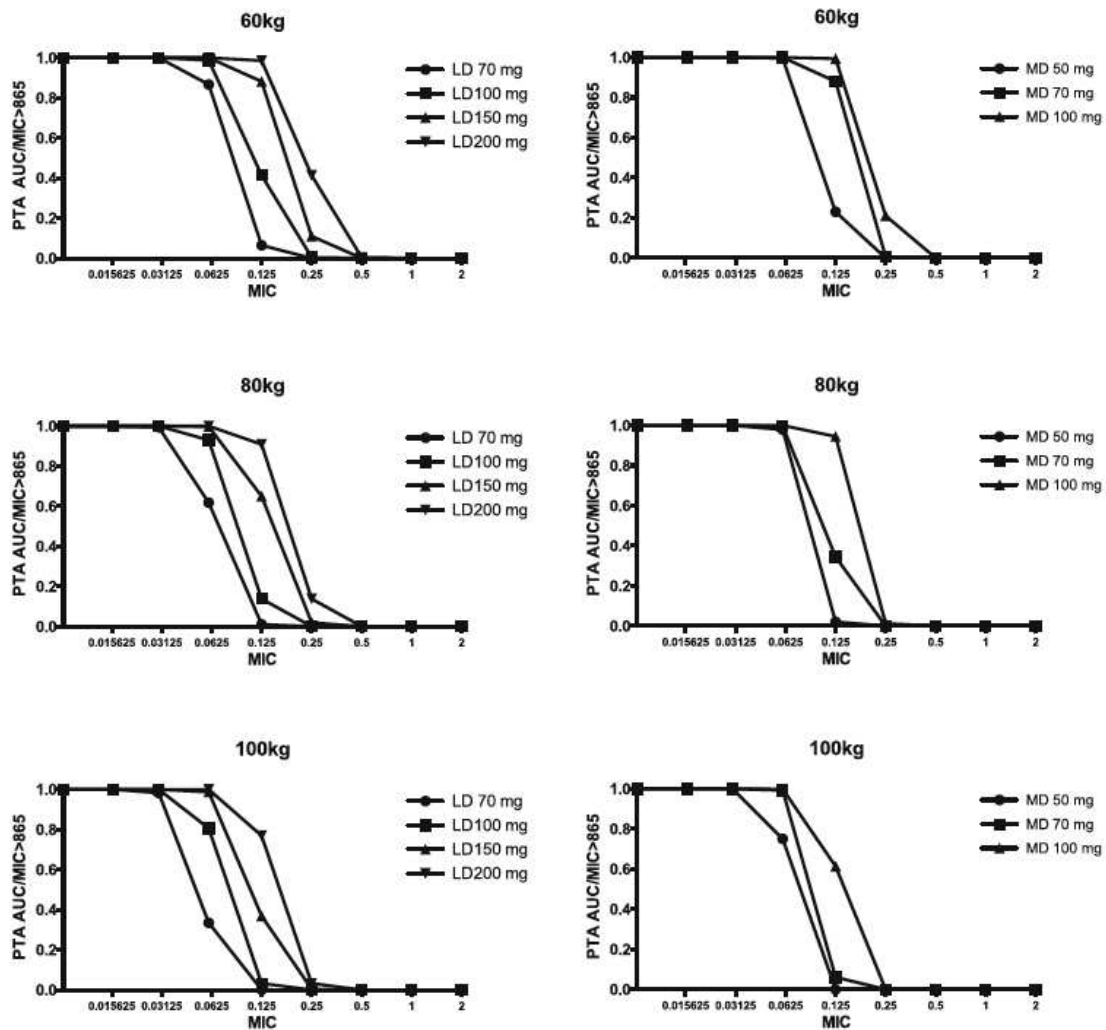


Fig. 3 Probability of target attainment of  $AUC/MIC > 865$  for various loading doses (left panels) and for a fixed loading dose of 100 mg followed by various maintenance doses (right panels) of caspofungin in patients with total body weight of 60, 80 and 100 kg.

$AUC$  area under the plasma concentration–time curve,  $LD$  loading dose,  $MD$  maintenance dose,  $MIC$  minimal inhibitory concentration,  $PTA$  probability of target attainment

distribution for *C. albicans* and *C. glabrata* are shown in Table 5.

#### 4 Discussion

This is the first population pharmacokinetic analysis of caspofungin focusing on critically ill patients undergoing CRRT. In the present model, the CRRT mode did not explain caspofungin pharmacokinetic variability in our population. In addition, based on population pharmacokinetic analysis

and Monte-Carlo simulations, higher than recommended loading doses achieved the predefined pharmacokinetic/PD targets for *C. albicans* ( $AUC_{24}/MIC > 865$  [25]) and *C. glabrata* ( $AUC_{24}/MIC > 450$  [25]). A 100 mg loading dose followed by a 50 mg maintenance dose for patients with a total body weight of  $\leq 80$  kg best achieved the pharmacokinetic/pharmacodynamic targets whilst a 100 mg loading dose followed by a 70 mg maintenance dose for patients with a total body weight of  $> 80$  kg was required to achieve pharmacokinetic/pharmacodynamic targets for *Candida* spp. with MICs up to 0.06 mg/L.

△ Adis

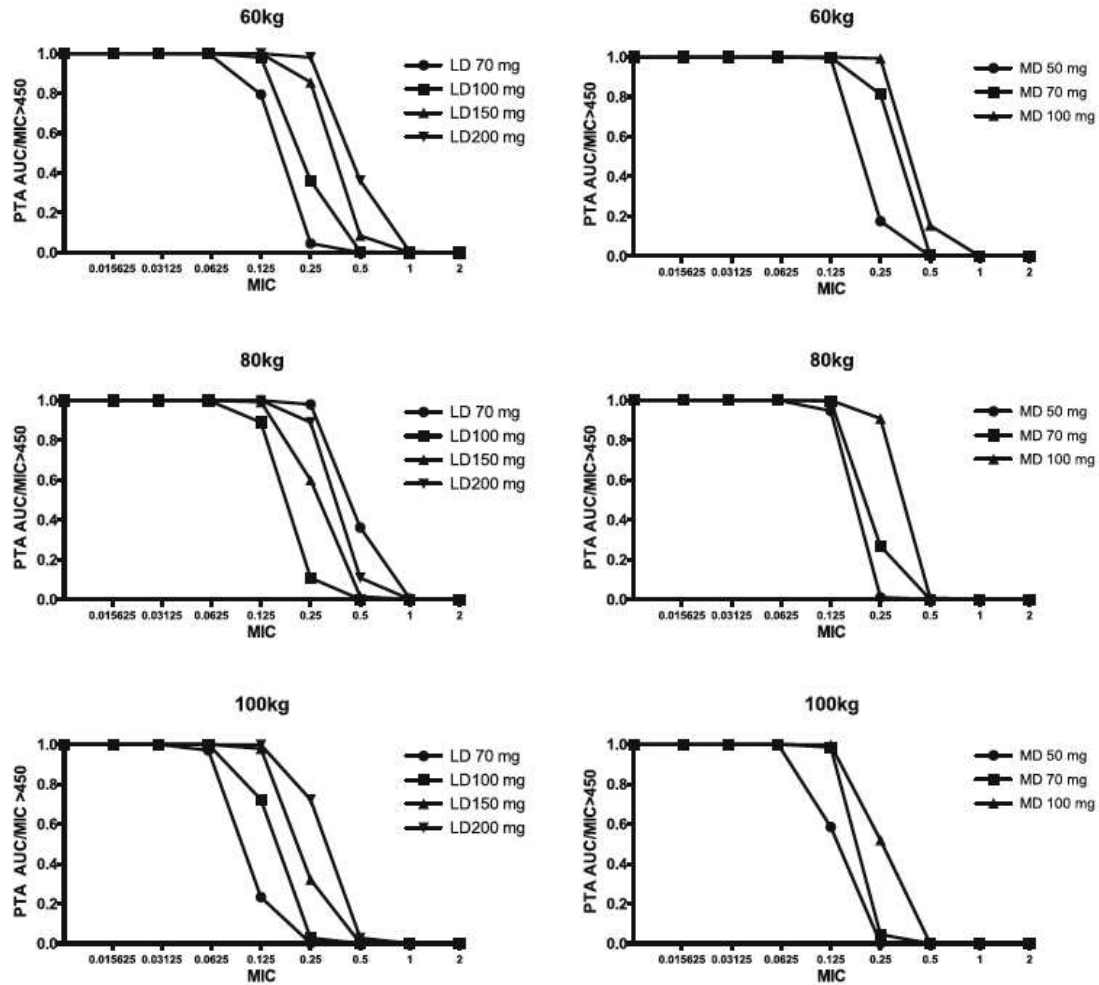


Fig. 4 Probability of target attainment of  $AUC/MIC > 450$  for various loading doses (left panels) and for a fixed loading dose of 100 mg followed by various maintenance doses (right panels) of caspofungin in patients with total body weight of 60, 80 and 100 kg.

*AUC* area under the plasma concentration–time curve, *LD* loading dose, *MD* maintenance dose, *MIC* minimal inhibitory concentration, *PTA* probability of target attainment

Whilst widely prescribed as a first-line antifungal therapy for invasive candidiasis, few data on caspofungin pharmacokinetics in ICU patients receiving CRRT are available. In the present study, we reported a very low caspofungin CL related to CRRT (1.25 and 1.09% for CVVH and CVVHDF, respectively), regardless of the mode applied. These results are in line with those reported by Weiler et al. [18] in patients receiving CVVH and CVVHD using different settings and membranes. When calculated from the sieving coefficient, Weiler et al. [18] found a caspofungin RRT CL of 0.008 (0.038) L/h, accounting for 1.8% of the total CL. When estimated from

haemofilter inlet and outlet concentrations (which takes into account the adsorption of the drug on the haemofilter), the CL was higher (0.061 [0.010–0.712] L/h) [18]. The caspofungin pharmacokinetic parameters were similar on and off CRRT. These findings as well as studies reporting similar caspofungin pharmacokinetic parameters in patients receiving or not receiving CRRT support the negligible effect of CRRT on caspofungin pharmacokinetics [12, 13]. Given its high protein binding (94–97%), it is not surprising that caspofungin is not significantly cleared by CRRT. Some adsorption on the membrane has been previously reported for echinocandins [11, 27];

△ Adis

**Table 5** Fractional target attainment for the various caspofungin doses for patients with body weights of 60, 80 or 100 kg against a minimal inhibitory concentration distribution for *Candida albicans* and *C. glabrata* [26]

Body weight (kg)	LD or MD	IV dose (mg)	<i>C. albicans</i> (%)	<i>C. glabrata</i> (%)
60	LD	70	85.7	96.5
		100	92.3	98.6
		150	97.4	99.3
		200	98.7	99.5
	MD (+LD 100 mg)	50	90.7	96.4
		70	97.3	98.0
		100	98.6	98.6
		150	95.0	99.0
		200	97.7	99.3
		70	98.0	98.3
80	LD	70	78.4	99.5
		100	88.0	97.5
		150	95.0	99.0
		200	97.7	99.3
	MD (+LD 100 mg)	50	88.2	95.3
		70	91.9	96.6
		100	98.0	98.3
		150	91.9	98.6
		200	96.2	99.1
		70	88.9	95.9
100	LD	70	70.5	90.0
		100	83.8	95.8
		150	91.9	98.6
		200	96.2	99.1
	MD (+LD 100 mg)	50	82.0	90.6
		70	88.9	95.9
		100	94.6	97.3

Doses not achieving the a priori probability of target attainment  $\geq 90\%$  of isolates are in italics  
 IV intravenous, LD loading dose, MD maintenance dose

however, this effect does not significantly affect caspofungin pharmacokinetics. Considering the low caspofungin CRRT-related CL, Weiler et al. [18] concluded that standard dosing regimens of caspofungin are appropriate in critically ill patients undergoing CRRT.

Based on the population pharmacokinetic analysis and Monte-Carlo simulations performed, our results showed that using recommended caspofungin dosing regimens (i.e. a loading dose of 70 mg followed by a maintenance dose of 50 mg for patients  $\leq 80$  kg and 70 mg for patients  $>80$  kg) led to sub-optimal achievement of therapeutic targets. In contrast to Weiler et al. [18], our study support the use of higher than recommended caspofungin loading doses in ICU patients to ensure adequate antifungal exposure in the first 24 h of therapy. Indeed, a loading dose of 100 mg followed by a maintenance dose of 50 mg for patients with a body weight  $\leq 80$  kg and a loading dose of 100 mg followed by a maintenance dose of 70 mg for patients with a body weight  $>80$  kg best achieved the caspofungin pharmacokinetic/pharmacodynamic targets for *C. albicans* and *C. glabrata* with MICs up to 0.06 mg/L. In septic patients, increased capillary permeability, low albumin concentrations and/or excessive fluid administration can alter the  $V_d$  of several antimicrobials [5]. Higher than standard loading doses can be required in critically ill patients with an increased  $V_d$  to achieve adequate exposure quickly. In the

present study, the central  $V_d$  was higher (9.35 ( $\pm 3.56$ ) L) than previously reported in healthy volunteers (4.09 ( $\pm 0.80$ ) L) and a non-ICU population (5.85 L, CV 28.8%) [28, 29]. For caspofungin, high dosing regimens have already been shown to be safe and well-tolerated in other patient groups [30, 31]. Higher loading doses should be considered in ICU patients due to the risk of under-exposure in the context of increased  $V_d$ .

While considering these results, two points should be highlighted:

- Given the lack of well-established clinical pharmacokinetic/pharmacodynamic targets and breakpoints, we used preclinical pharmacokinetic/pharmacodynamic targets for the two most representative *Candida* spp. to perform our simulations. Murine models of systemic candidiasis showed that  $AUC_{24}/MIC$  was the pharmacodynamic index that best predicted caspofungin efficacy [25, 32]. An  $AUC_{24}/MIC > 865$  for *C. albicans* and  $AUC_{24}/MIC > 450$  for *C. glabrata* associated with a  $1 \log_{10}$  kill/24 h were chosen as the pharmacokinetic/pharmacodynamic targets for our simulations [25].
- A high inter-laboratory variability using CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods and issues to adequately determine caspofungin MICs have been reported [33].

Therefore, the impact of increasing dosing regimens on the PTA is of great interest but MIC values should be interpreted carefully.

As did earlier studies, we observed a high caspofungin pharmacokinetic variability in this study. Nguyen et al. [34] reported great variability and increased caspofungin trough concentrations compared with healthy volunteers. However, inconsistent effects of the covariates on caspofungin pharmacokinetics have been reported in the literature to explain this variability. Nguyen et al. [34] found that a body weight >75 kg and albumin concentrations >23.6 g/L were estimated to decrease and increase caspofungin troughs by 0.6 and 0.25 mg/L, respectively. In contrast to this study, Muilwijk et al. [13] didn't find any correlation between caspofungin pharmacokinetics and body weight. In our study, total body weight was the main covariate that affected both CL and  $V_d$ . Similar correlations have been reported in a population of patients with invasive aspergillosis [29].

There are limitations that need to be declared regarding this study. Firstly, a larger sample size may have enabled inclusion of more covariates. However, we believe that weight is probably the main covariate that influences caspofungin dosing. Secondly, although measurement of the unbound caspofungin concentration would be of interest, as caspofungin is highly protein bound (94–97%) it was not feasible in this analysis. However, using free AUC/MIC ratios requires assumption of a value for protein binding that would strongly influence the results of the PTA. As protein binding may vary over time and between subjects in the ICU population, use of an assumed value could call the reliability of the results into question. Thirdly, we could not assess mechanistically whether the concentrations observed were caused by CRRT or non-CRRT CL because data on the CL of caspofungin into CRRT effluent was not available in this study; however, this limitation does not alter the end result of our dosing recommendations.

## 5 Conclusion

In critically ill patients receiving CRRT, no dosing adjustment for caspofungin is required, regardless of the CRRT mode applied. However, the results of this study suggest that higher than recommended loading doses (100 mg) are required to achieve caspofungin pharmacokinetic/pharmacodynamic targets in the first 24 h of therapy, whereas the recommended maintenance dose based on patient weight (50 mg for patients with a body weight of  $\leq 80$  kg and 70 mg for patients with a body weight of  $>80$  kg) seems adequate.

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## Compliance with Ethical Standards

**Ethics approval and consent to participate** Ethics approval was obtained from the local ethics committee in Nîmes, France (Comité de Protection des Personnes Sud Méditerranée III 2012.02.05). Written informed consent was obtained from either the patient or their nominated substitute decision maker.

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## 7. VALIDATION DU MODELE PK/PD

L'approche PK de population est une approche séduisante et source d'information riche sur le comportement d'un antibiotique en fonction de la population étudiée. Cette technique nécessite une bonne connaissance de la pharmacocinétique mais également de la clinique afin d'évaluer la plausibilité physiopathologique des relations établies entre les covariables et les paramètres PK. Il est prudent de se questionner sur la validité du modèle élaboré avant toute application pratique des posologies optimales définies par les résultats de cette analyse PK.

Plusieurs méthodes peuvent être utilisées pour évaluer la validité du modèle développé :<sup>102,103</sup>

### ***a) Validation interne***

La validation interne du modèle fait appel à une méthode de bootstrapping. A partir de la base de données constituée par n individus, il s'agit de tirer au sort les individus un à un avec remplacement de chaque individu dans le pool initial après tirage au sort. Une nouvelle base de données est donc constitué à partir de ce tirage au sort et le modèle développé est utilisé pour estimer les paramètres pharmacocinétiques, cette analyse étant répétée au minimum 200 fois et classiquement 1000 fois. La moyenne de chacun des paramètres PK sera calculée et comparée à la valeur obtenue avec la base de données originale. Une autre approche, le visual predictive check (VPC) consiste à superposer la distribution (intervalles de confiance autour des valeurs) des concentrations prédites aux valeurs des concentrations observées et de calculer la proportion de valeurs observées se trouvant en dehors de l'intervalle du 5<sup>ème</sup> – 95<sup>ème</sup> percentile.

### ***b) Validation externe***

La validation externe est probablement la méthode la plus reconnue et la plus robuste pour tester un modèle mais est également la plus coûteuse. Elle consiste à utiliser une nouvelle base de données provenant d'une autre étude et de tester les performances du modèle pour prédire les concentrations observées dans cette nouvelle population de patients. L'**article 7** s'intéresse à la validation externe à l'aide de la base de données de l'**article 2** d'un modèle PK développé pour la gentamicine chez des patients de réanimation.<sup>104</sup> Ce travail est le fruit d'une collaboration avec l'équipe d'Amsterdam dirigée par le Pr Van Hest.

**Article 7 : Performances prédictives d'un modèle PK de population de gentamicine dans deux populations distinctes de patients de réanimation.**

Dans cette démarche de validation externe, les bases de données PK associées aux covariables recueillies à partir de ces deux populations distinctes vont être successivement analysées par le modèle préalablement développé par l'équipe néerlandaise et les performances prédictives de ce modèle vont être comparées entre les deux populations.

Les performances prédictives du modèle sont évaluées à partir de l'erreur moyenne (EM) et la valeur absolue de l'erreur moyenne (AEM) comme reflet respectivement du biais et de la précision et définies comme suit :<sup>77,105</sup>

$$EM = \frac{1}{n} \sum_{j=1}^n (C_{pred} - C_{obs})$$

$$AEM = \frac{1}{n} \sum_{j=1}^n |C_{pred} - C_{obs}|$$

Lorsque l'intervalle de confiance à 95% de l'erreur moyenne comprend la valeur 0, le biais est considéré comme non significatif. Une valeur de précision de moins de 2,5 mg/L était considérée comme acceptable. Le modèle final initialement développé par l'équipe d'Amsterdam incluait l'albumine comme facteur affectant le Vd de la gentamicine et la

CICr et la présence d'EER comme facteur affectant la clairance de la gentamicine. Différentes variables évaluant la fonction rénale (diurèse totale journalière, créatinine plasmatique et CICr) avaient été testées pour développer ce modèle. Le modèle utilisé dans la validation externe a été adapté et retient l'albumine comme facteur affectant le Vd de la gentamicine et la diurèse totale journalière comme facteur affectant la clairance de la gentamicine.

Les performances prédictives obtenues dans les deux datasets sont présentées dans le tableau 3 ci-dessous :

	AMC Amsterdam (n=66)		CHU Nîmes (n=50)	
	Structural model	Final model	Structural model	Final model
Mean Error (mg/L)	0.35 (-0.11 – 0.81)	0.81 (0.33 – 1.30)	4.81 (4.00-5.62)	6.89 (5.92 – 7.81)
Mean Absolute Error (mg/L)	2.54 (2.26 – 2.82)	2.54 (2.21 – 2.86)	5.45 (4.72-6.17)	7.17 (6.27 – 8.07)

Tableau 3 : Performances prédictives du modèle structural et du modèle final avec covariables dans la population de l'AMC Amsterdam et du CHU de Nîmes.

Les performances prédictives du modèle développé pour l'adaptation posologique de gentamicine à Amsterdam s'avèrent médiocres dans la population du CHU de Nîmes, avec un biais significatif et une précision jugée comme inacceptable alors que ces performances dans la population d'Amsterdam sont bonnes.

Ces résultats posent la question de la robustesse du modèle et de son utilisation pour prédire les concentrations plasmatiques de gentamicine dans une population n'ayant pas servi à développer le modèle. Toutefois, deux explications peuvent être avancées pour cette mauvaise performance prédictive du modèle :

- Premièrement, bien que les populations dont sont issues les prélèvements plasmatiques soient toutes les deux des populations de patients de réanimation, la population d'Amsterdam présente des scores de gravité plus élevés ainsi qu'une proportion plus importante de défaillances rénales et d'EER. Ceci nous a amené à conclure à un comportement PK différent de la gentamicine dans ces deux populations, résultats confirmés par l'analyse des paramètres PK estimés dans chaque population (Tableau 4).

Parameter	Validation					
	Structural Model		AMC Amsterdam		CHU Nimes	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
CL not on CVVH (L/h/70 kg)	1.92	1.47 – 2.37	2.39	1.933 – 2.85	3.93	2.99 – 4.87
CL on CVVH (L/h/70 kg)	2.08	1.79 – 2.37	1.60	1.22 – 1.97	2.46	2.37 – 2.55
V1 (L/70 kg)	21.2	19.39 – 23.01	23.9	21.20 – 26.61	28	24.90 – 31.10
Q (L/h/70 kg)	2.26	1.58 – 2.94	0.625	0.17 – 1.08	1.68	0.02 – 3.34
V2 (L/70 kg)	18.9	16.12 – 21.68	6.47	3.02 – 9.92	12.8	7.06 – 18.54

Tableau 4. Estimations des paramètres PK de chaque population (AMC Amsterdam, CHU Nîmes) à partir du modèle structural préalablement développé.<sup>104</sup>

- Deuxièmement, cette validation externe met en exergue l'impact majeur joué par les covariables sur les prédictions du modèle. En effet, dans la base de données issue du CHU de Nîmes l'albumine n'était pas mesurée systématiquement lorsqu'un aminoside était

administré. Ceci a conduit à des données manquantes portant sur cette covariable et par conséquent, une moins bonne estimation du Vd de la gentamicine dans cette population.

**Conclusion : la validation externe d'un modèle est une étape indispensable avant la mise en application pratique de ce modèle pour l'adaptation posologique et la prescription individualisée d'antibiotiques. Le choix attentif du modèle doit porter sur les caractéristiques pharmacocinétiques de la population étudiée ainsi que sur les covariables retenues dans le modèle.**

**Article 7. Performances prédictives d'un modèle PK de population de gentamicine dans deux populations distinctes de patients de réanimation. *Soumission IJAA, rang B, impact factor : 4.3.***

**Predictive performance of a gentamicin population pharmacokinetic model in two Western populations of critically ill patients.**

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## **Abstract**

Before population pharmacokinetic (PK) models can be clinically applied to aid in dose selection, external validation of the model is warranted. The aim of this study was to assess the predictive performance of a published gentamicin population PK model in intensive care unit (ICU) patients in two independent populations of Western critically ill patients.

### **Methods**

Data from the same ICU as used for the earlier model development (Academic Medical Centre, Amsterdam (AMC)) and from the Centre Hospitalier Universitaire de Nîmes, (CHU Nîmes) were collected. Primary endpoints were bias and accuracy. The model was regarded as valid when bias was not significantly different from 0 and accuracy was equal to or less than 2.5 mg/L. Nonlinear mixed-effects modelling (NONMEM) was used for data analysis.

### **Results**

The AMC validation dataset consisted of 192 samples from 66 ICU patients and the CHU Nîmes dataset of 230 gentamicin samples from 50 ICU patients. The structural model could predict the gentamicin plasma concentrations in the AMC population with a non-significant bias (0.35, 95%CI: -0.11 – 0.81) and a sufficient accuracy of 2.5 mg/L (95%CI: 2.3 – 2.8). The gentamicin plasma concentrations were overpredicted in the CHU Nîmes population with a significant bias of 4.8 mg/L (95%CI: 4.00 – 5.62) and an accuracy of 5.5 mg/L (95%CI: 4.7 – 6.2).

### **Conclusion**

The model is valid for use in the AMC ICU population but not in the CHU Nîmes ICU population. This illustrates that caution is needed when using a population pharmacokinetic model in an external population.

**Keywords:** gentamicin, predictive performance, population pharmacokinetics, critical illness, hypoalbuminaemia



## 1. Introduction

Gentamicin is often included in empirical broad-spectrum antibiotic therapy for treatment of sepsis. As it has been shown that every hour delay in appropriate antibiotic administration is associated with a decreased survival rate of 7.6% in intensive care unit (ICU) patients, it is of great importance to administer the right dose as soon as possible to a septic patient. [1–3] In case of gentamicin, the dose is considered appropriate when a maximum gentamicin plasma concentration ( $C_{max}$ ) / minimum inhibitory concentration (MIC) ratio of 8 to 10 is achieved. This target had been associated with a faster clinical response and thus a larger probability of cure.[4–6] According to Dutch therapeutic drug monitoring (TDM) guidelines, a gentamicin  $C_{max}$  of 15-20 mg/L is considered therapeutic whereas French aminoglycoside dosing guidelines recommend targeting 30 to 40 mg/L.[7,8] Interindividual variability in gentamicin pharmacokinetics in ICU patients is however large, making the probability that a  $C_{max}/MIC \geq 10$  is reached with a starting dose of 5 mg/kg in only 27.3% for organisms with a MIC 1 mg/L.[9,10] Furthermore, a wide variety in trough concentrations ( $C_{min}$ ) is observed when gentamicin is administered once-daily, mainly caused by the large impact of variable renal function on the gentamicin clearance. Since a  $C_{min}$  below 0.5 to 1 mg/L are associated with a lower risk for nephrotoxicity, monitoring of the trough concentrations is recommended by some guidelines.[11,12]

Population pharmacokinetic (PK) models can help to understand the complex pharmacokinetics in critically ill patients and identify covariates that explain part of the interindividual variability (IIV). Such models can aid in selecting the right starting dose and optimizing individual dosing regimens. In an earlier study, such a population PK model was developed by Hodiamont et al. for gentamicin in ICU patients. Plasma albumin concentrations were identified as a significant covariate on the central volume of distribution and continuous venovenous hemofiltration (CVVH) and total daily diuresis (TDIU), as measure of renal function, as covariates on clearance.[13] External validation of this model is necessary to confirm whether this model can reliably be used for calculation of the appropriate gentamicin (starting) doses. The aim of this study was to externally validate the previously developed population PK model by evaluating its predictive performance in cohorts from two different ICUs. A second objective of the study was to validate the effect of albumin on volume of distribution of gentamicin in ICU patients to ascertain that this covariate could aid in selecting the initial dose.

## 2. Materials and methods

### 2.1 Patients and data

For the external validation of the population PK model, datasets from two ICU populations were used. For the first cohort, data were collected at the ICU of the Academic Medical Centre (AMC) Amsterdam, The Netherlands, between 7 November 2016 and 15 March 2017 in a prospective observational design. All adult ( $\geq 18$  years) patients admitted to the ICU receiving gentamicin were included, if at least one gentamicin concentration measurement was available. Pregnant patients and patients on hemodialysis were excluded. Following the Dutch law (WMO, article 1), ethical approval was not needed as only anonymous data from routine clinical care was used in this study.

The patients received a gentamicin starting dose of 5 mg/kg total body weight when suffering from sepsis and 3 mg/kg total body weight for endocarditis treatment. Part of the samples for the dataset originated from therapeutic drug monitoring (TDM) which is routinely conducted at the ICU of the AMC. To verify whether the  $C_{max}$  was therapeutic (15-20 mg/L) a sample is drawn one hour after start of the first gentamicin infusion. Furthermore, a follow-up blood sample is drawn the next morning around 6 a.m., which is used to estimate when the gentamicin concentrations drop below 1 mg/L and thus when a next dose can be administered. Three times a week new follow-up samples are collected to check whether the dosing interval is still appropriate. Additionally, the dataset consisted of scavenged blood from blood gas samples drawn in the ICU patients treated with gentamicin. These samples were stored at room temperature for a maximum of 96 hours. Thereafter they were centrifuged at 4000 rpm for 5 minutes to separate the blood plasma, which was stored in the  $-80$  °C freezer and analyzed within 100 days.[14] Times of gentamicin administration and of blood sample collection were witnessed during the day where possible and otherwise collected as registered in the electronic patient data information system of the hospital. Moreover, the duration of infusion was witnessed, as this duration often differs from the 30 minutes infusion prescribed in the protocol.

Gentamicin plasma concentrations were measured with a Fluorescence Polarization Immunoassay (type: Cobas Integra 400+ auto analyzer). The Cobas has a lower limit of quantification (LLOQ) of 0.5 mg/L and the accuracy was 96.1%, 104.0% and 103.1% at concentrations of 2.16, 4.86 and 7.88 mg/L respectively. At these concentrations the intraday

precision was 1.24%, 0.95% and 1.42% and the interday precision was 2.91% 2.54% and 3.35% respectively.

The following patient characteristics: age, sex, total body weight (TBW), length, creatinine level, albumin plasma concentration, TDIU, application of CVVH and the severity of disease described by the sequential organ failure assessment (SOFA) score, were collected from the electronic patient data information system of the hospital. An albumin level was denoted as missing when no albumin level was known 24 hours before or after a gentamicin infusion or a gentamicin sample collection whereas SOFA score and TDIU were denoted as missing when no value was recorded 12 hours before or after a gentamicin infusion or a gentamicin sample collection. The ideal body weight (IBW) was calculated according to equation 1 and 2. The dataset thus created is referred to as the AMC data.

$$IBW \text{ men (kg)} = 50 + 0.91 \times (\text{length (cm)} - 152) \quad (1)$$

$$IBW \text{ women (kg)} = 45 + 0.91 \times (\text{length (cm)} - 152) \quad (2)$$

The second data set came from the Centre Hospitalier Universitaire (CHU) in Nîmes, France. These data are described in detail elsewhere.[7,15] In short, the data were collected in ICU patients ( $\geq 18$  years) that received gentamicin in one of the following two periods: 2 June until 29 November 2013 or 30 October 2014 until 10 March 2015. The data from the two periods were combined into one dataset as there were only statistically significant differences ( $p$ -value  $< 0.05$ ) between both periods in age and SOFA score, which were not identified as significant covariates in the previously developed model, thus no influence on the predictive performance was expected. Gentamicin was administrated in a 30-minute intravenous infusion and  $C_{max}$  and  $C_{min}$  were routinely measured with an automated Immunoassay with a Cobas C system (LLOQ=0.4 mg/L). Information on albumin concentrations, application of CVVH, creatinine concentrations, SOFA score, length, height, age and sex was collected. IBW was calculated following equation 1 and 2. This dataset is referred to as the CHU Nîmes data.

## 2.2 Data analysis

With the use of the two datasets the previously developed population PK model for gentamicin was validated using Bayesian estimation in NONMEM (v7.3.0, Icon Development Solutions, Ellicott City, MD, USA).[13] The population PK parameters were fixed to the final estimates of the previously developed model and maximum evaluations (MAXEVAL) was set to 0. The predictive performance of this model without covariates, referred to as the structural model, as well as the predictive performance of the model with the covariates, referred to as the final model, was examined.

The structural population PK model is a two-compartment model with allometrically scaled PK parameters to an IBW of 70 kg. Furthermore, a clearance parameter was separately estimated for patients on and off CVVH. IIV was estimated on the central volume of distribution and on both clearance parameters, using a log-normal distribution. Interoccasion variability (IOV) was estimated on the clearance parameter off CVVH. The final model included a negative association between albumin level and the central volume of distribution and a positive correlation between TDIU and clearance off CVVH. All details on the structural and final model can be found in reference 13.

The predictive performance of the model was evaluated by comparing the population predicted concentrations (Cpred) with the observed concentrations in the datasets (Cobs). Primary endpoints for the predictive performance were the mean error (ME, equation 3) and mean absolute error (MAE, equation 4) calculated as measurements for bias and accuracy. [16,17]

$$ME = \frac{1}{n} \sum_{j=1}^n (C_{pred} - C_{obs}) \quad (3)$$

$$MAE = \frac{1}{n} \sum_{j=1}^n |C_{pred} - C_{obs}| \quad (4)$$

Where n represents the number of observations of all individuals. If 0 was included in the 95% confidence interval (CI) of ME, no significant bias was present. When this was the case and a MAE of  $\leq 2.5$  mg/L was obtained, the model was regarded as valid. The MAE cut-off of 2.5 mg/L was chosen because a deviation of 2.5 mg/L from 17.5 mg/L, the middle of the therapeutic window of Cmax (15-20 mg/L), still results in a therapeutic Cmax and as such in a lower than 50% chance of a false positive indication for dose adjustment. To visualize the predictive performance Blant-Altman plots are made and Visual Predictive Checks (VPCs) are made. [18] PsN (v3.5.3, Uppsala University, Sweden) was used for the performance of VPCs. [19]

For the secondary objective of this study, the AMC data was fitted to the previously developed final model with and without albumin as a covariate on central volume of distribution (V1), using the First Order Conditional Estimation method with Interaction (FOCE+I) as implemented in NONMEM. Pirana (v2.9.4., Software & Consulting BV, The Netherlands) was used for model management. Missing albumin values were ignored in the estimation of the association between the covariate and the PK parameter, as described earlier [20]. When the objective function value (OFV), calculated based on the likelihood ratio test, increased with 3.84 units or more for the final model without albumin relative to the final model with albumin, albumin was regarded as having a statistically significant association

with V1 ( $p < 0.05$  and  $\chi^2$  –distribution and 1 degree of freedom). Furthermore, an increase in the estimate of IIV in V1 was taken into account as an indication that less IIV was explained without this covariate. IIV is expressed as the coefficient of variation (CV) and was calculated by taking the square root of  $(\exp(\omega^2)-1) * 100$ , where  $\omega^2$  is calculated by NONMEM. When albumin was found to be of significant influence on the central volume of distribution (V1), Cmax and V1 were plotted against albumin to visualize this association. The Cmax was calculated as the individual prediction of the gentamicin concentration at 0.5 hours after administration. Only the Cmax and V1 of the first dose are taken into account, as subsequent doses are also influenced by TDM.

### 2.3 Statistics

Statistical tests were performed in SPSS Statistics (v23, IBM, USA). For continuous distributed parameters the unpaired T-test was used. The Mann Whitney U test was executed when continuous data were non-normally distributed. Categorical parameters, such as sex and mortality rate, were analyzed using the Chi-square test. A p-value  $< 0.05$  was regarded as statistically significant.

## 3. Results

### 1. Data

For the AMC data, 66 patients that received in total 122 gentamicin doses were included. One patient was excluded because of the use of hemodialysis. A median of 1 dose was administered per patient with a range of 1 to 7. The AMC data consisted of 192 gentamicin concentration-time samples. Of these, 131 (68%) were routinely collected samples during TDM and 61 (32%) were collected from scavenged blood samples. On average 2.9 samples were measured per patient, with a median of 1 sample per dose interval (range 1 to 8). Especially those patients with poor kidney function and thus likely low gentamicin clearance had more than 1 sample per dosing interval. The number of concentrations below the limit of quantification (BLQ;  $< 0.5$  mg/L) was 15, ie. 7.8% of all samples, and these were excluded. Forty-five patients received gentamicin for the treatment of sepsis and 7 for endocarditis. The indication was unknown in the other patients ( $n=14$ ). The parameters IBW, CVVH, albumin and TDIU that were used in the previously developed model, were respectively 20%, 0%, 21%, 0% missing.

The CHU data consisted of 50 patients that received a total of 149 gentamicin doses (median 3 doses/patient; range 1-6). This dataset consisted of 230 gentamicin concentration-time samples. The number of samples ranged from 1 to 11 per patient (median 5), with a median of 2 samples per dose interval (range 1 to 5). Of these concentrations 26 (11.3%) were BLQ

(< 0.4 mg/L), therefore they were excluded. The covariates IBW, CVVH, albumin and TDIU that were used in the final model, were respectively 0%, 0%, 71% and 14% missing. In Table 1 the patient baseline characteristics from the AMC data and the CHU data are presented.

**Table 1: Patient characteristics at baseline**

	AMC Amsterdam (n=66)	CHU Nîmes (n=50)	P-value
Female [n (%)]	13 (20)	21 (42)	0.091
Age (years)	64 (55-73)	62 (49-75)	0.614
Mean dose (mg/kg body weight)	4.8 (4.7-5.1)	6.3 (5.2-7.5)	0.0
Total body weight (kg)	77.6 (67.4-89.5)	72.0 (59.1-87.5)	0.198
Ideal body weight (kg)	69.1 (60.5-74.6)	62.3 (57.0-66.4)	0.0
Height (cm)	174 (168-180)	168 (161-170)	0.01
SOFA score	9 (6-11)	5.5 (3-9)	0.0
CVVH [n (%)]	9 (14)	1 (2)	0.027
Serum creatinine ( $\mu$ mol/L)	112.5 (77.8-181.8)	87 (57-114.5)	0.02
Total daily diuresis (ml)	1125 (503 -2128)	1422 (721 -2150)	0.22
Albumin (g/L)	25 (19-31)	28.7 (25.1-32.8)	0.002
Death during ICU admission [n (%)]	12 (18)	4 (8)	0.098

*Values are expressed as median (interquartile range), unless stated otherwise. SOFA: Sequential Organ Failure Assessment, CVVH: continuous venovenous hemofiltration*

### 3.2 Predictive performance

Table 2 presents the ME (bias) and the MAE (accuracy) for the structural and the final model of the AMC data and the CHU data. The validation of the structural model using the AMC data yielded a statistically non-significant bias of 0.35 mg/L (95% CI: -0.11 – 0.81). The MAE was 2.54 mg/L (95%CI: 2.26 – 2.82) and thus equalled the prior set cut-off. For the final model (addition of the covariates albumin and TDIU) a small significant bias was found but the accuracy remained the same.

Validation of the structural model with the CHU data resulted in an upward bias of 4.81 mg/L, which was significantly different from 0 (95% CI: 4.00 – 5.62). Furthermore, less accurate predictions were found, as the MAE was 5.45 mg/L. The predictive performance of the final model was not better as it yielded in a bias of 6.89 mg/L (95%CI: 5.92 – 7.81) and an accuracy of 7.17 mg/L. The prior set goals were not reached when the CHU data was fitted with the earlier developed model.

The predictive performance is visualized in the Bland Altman plots in Figure 1. These plots, as well as the VPCs in figure 2, indicate that the model can estimate the gentamicin concentrations without bias and reasonable accuracy in the AMC population, but that the concentrations are overpredicted in the CHU population. The VPC is also indicating that in both populations the models are overestimating the IIV. However, this overestimation is larger in the CHU population.

**Table 2: Predictive performance of the model using population predictions**

	AMC Amsterdam (n=66)		CHU Nimes (n=50)	
	Structural model	Final model	Structural model	Final model
Mean Error (mg/L)	0.35 (-0.11 – 0.81)	0.81 (0.33 – 1.30)	4.81 (4.00-5.62)	6.89 (5.92 – 7.81)
Mean Absolute Error (mg/L)	2.54 (2.26 – 2.82)	2.54 (2.21 – 2.86)	5.45 (4.72-6.17)	7.17 (6.27 – 8.07)

*Values are expressed as mean (95% confidence interval)*

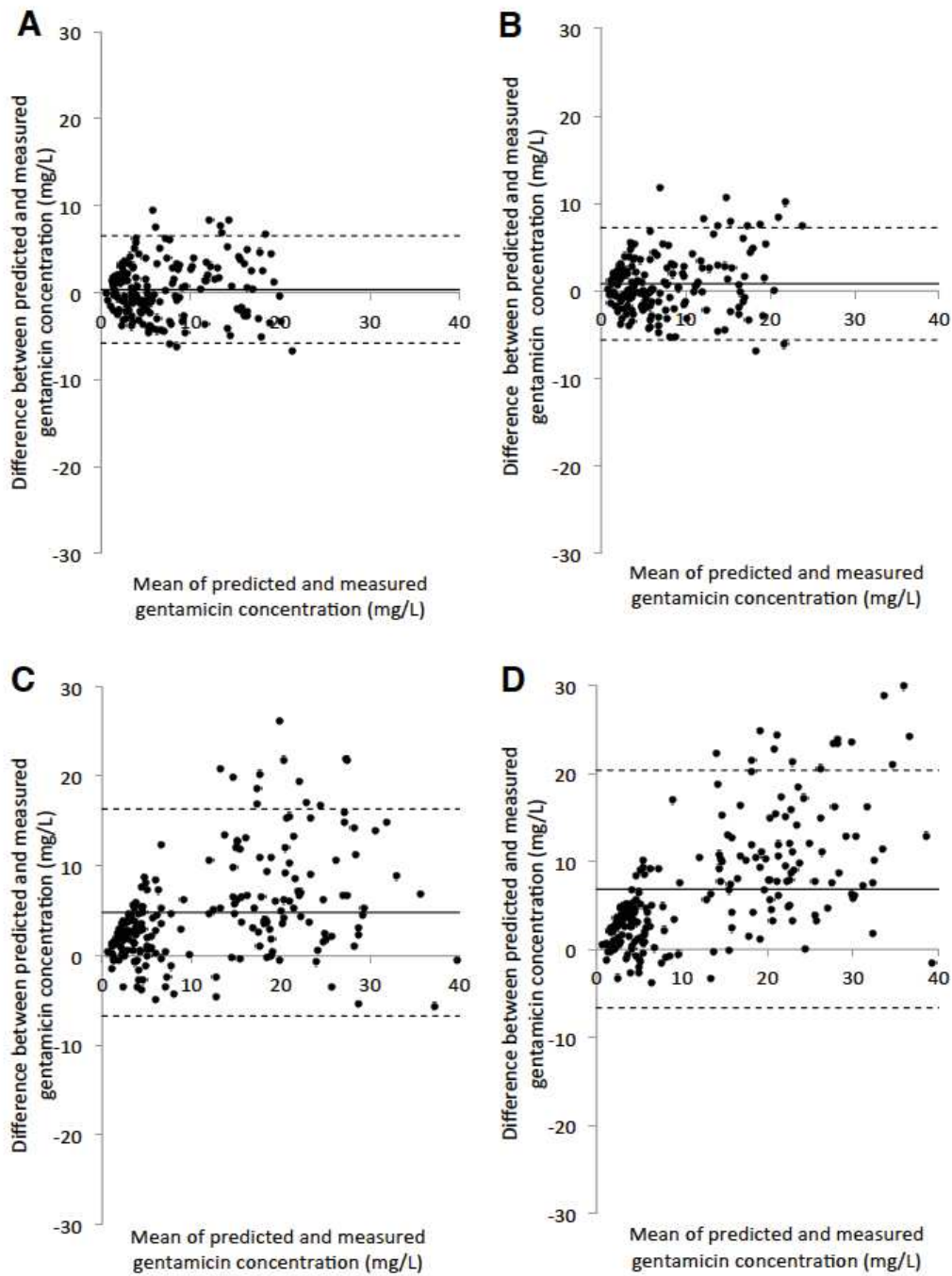


Figure 1: Bland Altman plots of the predictive performance of the previously developed model based on (A) the AMC data predicted by the structural model, (B) the AMC data predicted by the final model, (C) the CHU data predicted by the structural model and (D) the CHU data predicted by the final model. The differences between the population predicted and measured concentrations are plotted against the mean of the population predicted and measured gentamicin concentration. The dotted lines represents the  $\pm 1.96$  standard deviation and the solid line the mean error.



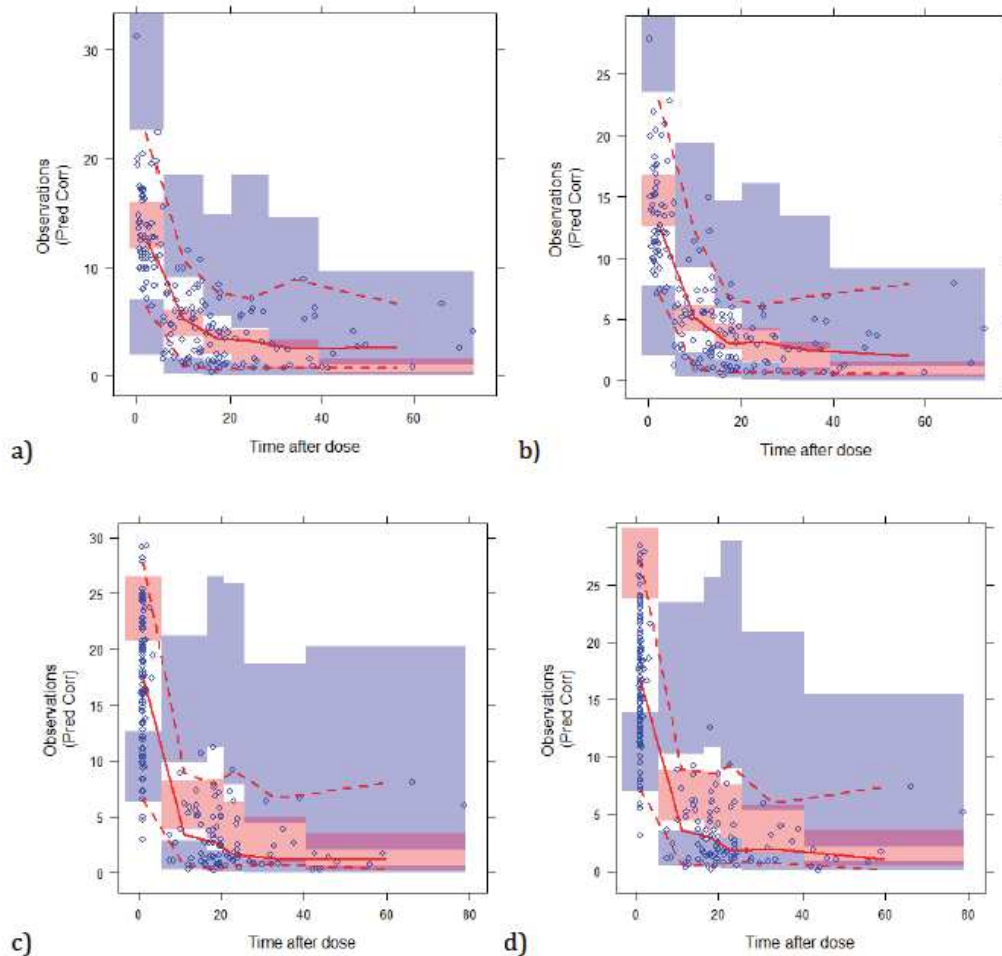


Figure 2: Prediction corrected visual predictive checks of the validation of the original model with (a) the data from the AMC ICU population using the structural model, (b) the data from the AMC ICU population using the final model, (c) the data from the CHU ICU population using the structural model and (d) the data from the CHU ICU population using the final model. The solid and dotted red lines show respectively the median, 5 and 95 percentiles of the measured concentrations. The red box indicates the 95%CI of the median of the predicted concentrations and the blue boxes the 95% CI of the 5 and 95 percentiles of the predicted concentrations. A model shows adequate predictive performance when the solid and dotted lines in the VPC run through the red and blue boxes respectively. IIV is overestimated when less than 5% of the concentration points are outside the blue boxes on both sides.

Furthermore, a posthoc analysis was used to test to what extent the PK of gentamicin from the present validation study were comparable to the PK of gentamicin from the model-building ICU population. For this purpose, both validation datasets were fitted ( $MAXEVAL > 0$ ) to the structural model using FOCE+I. The final population parameter estimates from the

previously developed model served as initial estimates. The newly estimated pharmacokinetic parameters were compared with the parameter estimates of the previously developed structural model and their 95%CI. Table 3 shows that the mean CL (both off and on CVVH) and the mean distribution volumes (V1 and V2) as estimated with the CHU data are higher and outside the 95%CI of the corresponding parameter estimates from the previously developed model. This is also the case when the parameter estimates obtained when fitting the CHU data are compared with the parameter estimates and their 95%CI obtained with the AMC data. This is consistent with the overprediction seen when validating the model with the CHU data.

**Table 3: Pharmacokinetic parameter estimates of the prospective AMC ICU and CHU ICU population when the collected data are fitted with the previously developed structural model.**

Parameter	Validation					
	Structural Model [14]		AMC Amsterdam		CHU Nimes	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
CL not on CVVH (L/h/70 kg)	1.92	1.47 – 2.37	2.39	1.933 – 2.85	3.93	2.99 – 4.87
CL on CVVH (L/h/70 kg)	2.08	1.79 – 2.37	1.60	1.22 – 1.97	2.46	2.37 – 2.55
V1 (L/70 kg)	21.2	19.39 – 23.01	23.9	21.20 – 26.61	28	24.90 – 31.10
Q (L/h/70 kg)	2.26	1.58 – 2.94	0.625	0.17 – 1.08	1.68	0.02 – 3.34
V2 (L/70 kg)	18.9	16.12 – 21.68	6.47	3.02 – 9.92	12.8	7.06 – 18.54

*Estimates are expressed as means. CI: Confidence interval, CL: clearance, CVVH: continuous venovenous hemofiltration, V1: central volume of distribution, Q; intercompartment clearance, V2: peripheral volume of distribution.*

### 3.3 Influence of plasma albumin concentration

To validate the association between albumin concentration and V1, the AMC data were fitted to the final model with and without albumin as a covariate on V1. This was not done with the CHU data as 71% of the albumin data was missing in that dataset. The OFV was 7.782 units higher in the final model without albumin concentration as a covariate on V1 (p-value <0.01 in a  $\chi^2$ -distribution with one degree of freedom). Furthermore, an increase in the estimate of the IIV in V1 from 32.4% to 36.3% was observed. The association between albumin concentration and V1 as well as the resulting effect on the Cmax is shown in Figure 3. It can be seen that serum albumin concentrations <20 g/L are associated with a low and often sub therapeutic Cmax.

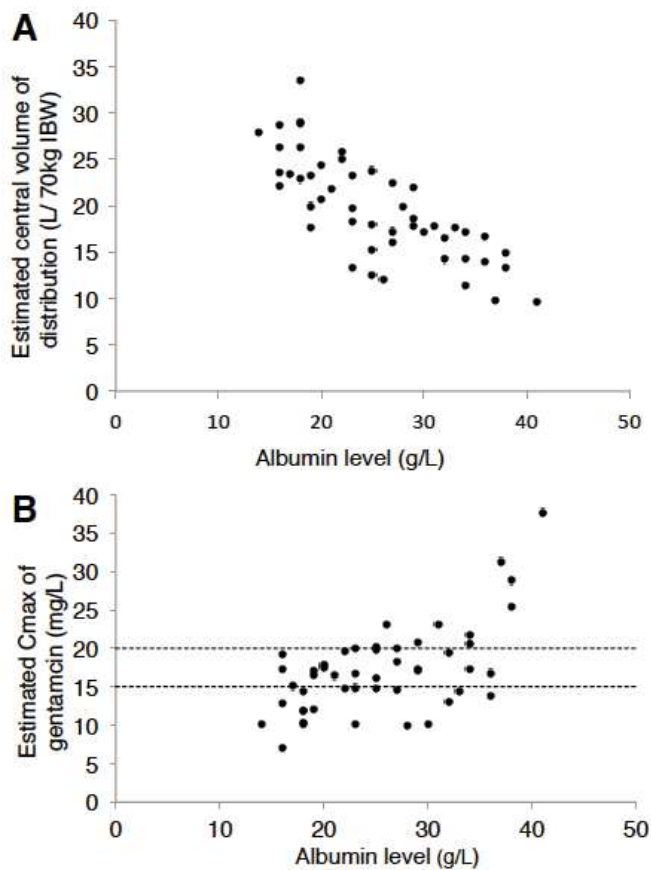


Figure 3: Albumin concentration in relation to (a) the estimated central volume of distribution (V1) of gentamicin and the (b) estimated peak concentration (Cmax) at 0.5 h after gentamicin administration, after fitting the AMC data to the final model. Only the Cmax and V1 of the first dose are presented. The dotted lines represent the therapeutic window for Cmax of 15 to 20 mg/l.

#### 4. Discussion

The predictive performance of a previously developed population PK model of gentamicin in ICU patients and the influence of albumin on gentamicin C<sub>max</sub> that was identified during development of that model were tested in two different populations of ICU patients. The prospectively collected AMC data, could be sufficiently predicted by the model, as shown by a ME that was not statistically significantly different from 0 and an MAE of 2.5 mg/L, but a large overprediction (statistically significant ME and MAE > 2.5 mg/L) was observed when predicting the concentrations observed in the CHU population. Low serum albumin concentration were associated with a larger central volume of distribution and thus with lower gentamicin C<sub>max</sub> in the AMC data.

A strength of this validation study was the fact that two independent datasets from different countries including patients with a different casemix. These datasets were selected with the assumption that these would be representative for the Western ICU population. A valid model would have been capable of predicting both the AMC and the CHU data appropriately. Another strength was the prospective collection of the AMC data, which enabled to closely witness the timing of the sample collection and gentamicin administration during the day. This will have contributed to the quality of the data and adds to a reliable data analysis. This was also reflected in the small proportional residual error of 11% estimated by NONMEM when the AMC data was fitted to the structural model. Furthermore, it resulted in few missing covariate data.

A limitation of this study was the fact that the CHU data were primarily collected with another aim. Although the CHU data were collected prospectively, the administration and sample collection times were not witnessed in real life and sample collection was done as part of routine clinical practice. Although this limitation, which is expected to contribute to random noise in the data, may have contributed to the inaccurate predictions of the CHU data, it cannot explain the structural upward bias in the prediction of the CHU data. Another consequence of the limitation that the data were primarily collected for another purpose, is the high percentage of missing covariates, in particular 71% of albumin concentrations were missing. Therefore the CHU data could not be used to verify the influence of albumin on V<sub>1</sub> and gentamicin C<sub>max</sub>.

The results show that the AMC data could be adequately predicted, while the ME was statistically significantly different from 0 and that MAE was larger than the a priori set cut-off of 2.5 mg/L when the CHU data were predicted with the structural model. Whether the observed bias and accuracy can be regarded as high or low is difficult to assess as no other studies that externally validated a population PK model for gentamicin in critically ill patients

could be identified in literature. Nevertheless, the ME and MAE observed with the CHU data seem to imply that the PK of gentamicin in the CHU ICU population is different from the AMC ICU population, which was confirmed when both datasets were used to estimate the population PK parameters (table 3). The estimate for clearance is higher in the CHU population, likely due to an overall higher renal function observed in this population. In comparison with the CHU data and with reports from other Western ICU populations the clearance of the AMC population seems quite low.[9,21] Furthermore also higher volumes of distribution were found, which cannot easily be explained mechanistically. Nonetheless, it is an indication that the CHU ICU population has different PK than the AMC ICU population. A possible explanation could be that the ICU population of the CHU was overall less ill, as lower SOFA-scores, lower mortality rates and better renal function were observed. However a lower volume of distribution in the CHU population would then a priori be suspected instead of a higher one, as Triginer et al. showed that higher gentamicin distribution volumes were found when the illness was more severe.[22] The volumes of distribution found of the CHU and AMC populations are in the range of earlier studies. [9,21,23]

The results of this validation indicate that the previously developed model cannot simply be used in other ICUs and that prior validation of the model is recommended with data from the population in which the model is intended to be used. Overall it implies that caution is needed when using population PK models developed based on data from other hospitals, even if the target population seems to belong to the same population as the one used to develop the model.

A remarkable result was that the final model is predicting the AMC data with comparable bias and accuracy in comparison with the structural model, while the CHU data were predicted less accurate and with more bias, while less bias and improved accuracy would be expected when covariate information is added to the model. It is suspected that this was mainly caused by the used measure for kidney function: total daily diuresis. This parameter was found second best in predicting the gentamicin clearance during development of the previous model after creatinine clearance (CalcCLcr) calculated based on a 6-hour urine portion. This hypothesis is strengthened by the observation that when TDIU was excluded from the final model fitted to the CHU data, the rise of OFV was only 3.65, which is a statistically non-significant increase. This indicates that total daily diuresis does not explain variability in the current data. The OFV rise was also non-significant (3.15 units) in case of excluding TDIU from the final model fitted with the AMC data. Unfortunately, CalcCLcr data were not available for this study, although it could be suspected that better predictions would be obtained when using CalcCLcr.

Albumin was found to significantly improve the fit of the model when using the AMC data and an association between albumin concentration and the volume of distribution of gentamicin could be supported. Following this association, the previous study of Hodiamont et al. showed that a sub-therapeutic C<sub>max</sub> in those patients with extremely low albumin concentration of <15 g/L.[13] Unfortunately, these extremely low C<sub>max</sub> values were barely observed in our study population. Nevertheless, an association was found and this covariate may aid in selecting the right gentamicin dose in ICU patients, e.g. by measuring the C<sub>max</sub> early in the course of treatment in ICU patients with serum albumin concentration <20 g/L to ascertain C<sub>max</sub> target exposure, or by prescribing at least 6 mg/kg in patients with albumin levels <20 g/L, especially when TDM is not conducted. This recommendation is strengthened by the fact that previous studies also have observed an negative association between the distribution volume and serum albumin concentrations in patients with pleural effusions, patients with hematological malignancies and intensive care patients receiving gentamicin.[13,24,25]

## **5. Conclusion**

This external validation study shows that the previously developed gentamicin population PK model for critically ill patients can predict gentamicin concentrations without bias and with acceptable accuracy in the ICU population admitted to the hospital where data for model development originated from (AMC, Amsterdam, The Netherlands). However the model overpredicts gentamicin concentrations in an ICU population from another Western hospital (CHU, Nîmes, France). Therefore, the model may not easily be used in other western ICU populations. In general, prior validation of population PK models with data from the population in which the model is intended to be used is recommended.

In addition, the negative association of albumin concentrations with the central volume of distribution of gentamicin in ICU patients was confirmed. This association implies that hypoalbuminaemia may result in a C<sub>max</sub> below the targeted range (<20 mg/L).

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## 8. LIMITES DE L'ANALYSE PK DE POPULATION

L'analyse PK de population présente un certain nombre d'avantages, comparée à l'approche PK individuelle. Toutefois, il est important d'en connaître les limites avant de débiter une étude portant sur la PK d'une molécule. Les principaux avantages et inconvénients sont listés dans le tableau 5 :

Avantages	Inconvénients
<ul style="list-style-type: none"><li>-Réduit le nombre de prélèvements par patient</li><li>-Possibilité d'analyser des données éparses</li><li>-Etudes de populations à risque (insuffisant rénal, âge extrême)</li><li>-Evaluer la variabilité interindividuelle et interoccasion</li><li>-Permet d'inclure des patients ayant reçu des doses et des voies d'administration différentes</li><li>- Détection et quantification des caractéristiques individuelles influençant les paramètres PK, possibilité d'individualiser la posologie</li><li>- Méthode reconnue par les instances réglementaires du médicament</li></ul>	<ul style="list-style-type: none"><li>- Logiciel d'utilisation complexe</li><li>- Coûteuse en temps</li><li>- Echech de l'analyse sur données éparses difficilement rattrapable</li><li>- Exhaustivité du recueil des covariables</li><li>- Technique de validation non standardisée</li></ul>

Tableau 5. Avantages et inconvénients d'une analyse PK de population.

Dans l'**article 8**, nous avons expérimenté les difficultés pouvant émaner d'un plan expérimental inadapté à l'analyse PK de population.

**Article 8 : Analyse PK traditionnelle de la piperacilline-tazobactam administrée en perfusion continue dans une population de patients septiques sous CVVH vs CVVHDF. IJAA, rang B, impact factor 2016 : 4.3.**

Dans ce travail, portant sur l'impact du sepsis et de l'EERc sur la PK de la piperacilline-tazobactam administrée en perfusion continue, les données recueillies n'ont pas permis de développer un modèle PK de population et nous avons donc choisi une approche individuelle non compartimentale. Le schéma expérimental de prélèvements n'a pas

permis d'estimer de façon précise et non biaisée le Vd de la pipéracilline du fait de données trop éparses au moment de la dose de charge. Toutefois, l'analyse PK individuelle a permis de mettre en évidence l'intérêt de la perfusion continue de pipéracilline-tazobactam au cours de l'EERc. En effet, elle permet d'obtenir des concentrations plasmatiques au-dessus de la CMI pendant 100% du temps d'administration y compris lorsque l'on considère les CMI les plus élevées. Les résultats de cette étude sur une faible cohorte de patients sous EER sont concordants avec les études conduites par l'équipe de Jason Roberts et Jeffrey Lipman (University of Queensland, Brisbane, Australie) qui ont mis en évidence un bénéfice de l'utilisation de la perfusion prolongée chez les patients de réanimation.<sup>106-108</sup>

Article 8 : Analyse PK traditionnelle de la piperacilline-tazobactam administrée en perfusion continue dans une population de patients septiques sous CVVH vs CVVHDF. *IJAA*, rang B, impact factor 2016 : 4.3.

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Short Communication

## Impact of renal replacement modalities on the clearance of piperacillin-tazobactam administered via continuous infusion in critically ill patients



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### ABSTRACT

This prospective pharmacokinetic study aimed to compare the clearance of piperacillin-tazobactam administered as a 24-h continuous infusion between continuous venovenous haemodiafiltration (CVVHDF) and continuous venovenous haemofiltration (CVVH) applied at equal dose in critically ill patients.

A loading dose of 4.5 g of piperacillin-tazobactam followed by a continuous infusion (500 mg/h) was administered to patients randomized to receive CVVHDF or CVVH. Serial pre- and postfilter blood samples were drawn during an 8-h sampling interval. Piperacillin plasma concentrations were measured using a validated chromatography method. Piperacillin pharmacokinetics were calculated using a non-compartmental approach.

In total, 212 piperacillin plasma concentrations were determined. Median [interquartile range (IQR)] total piperacillin clearance was 7.5 (5.9–11.2) L/h in the CVVHDF group and 4.7 (4.5–9.6) L/h in the CVVH group ( $P=0.21$ ). Median (IQR) piperacillin clearance related to continuous renal replacement therapy (CRRT) was 3.0 (2.7–3.2) L/h in the CVVHDF group and 2.6 (1.9–3.0) L/h in the CVVH group ( $P=0.29$ ). Mean (standard deviation) steady state concentrations were 68.4 (25.8) mg/L in the CVVHDF group and 89.1 (35.6) mg/L in the CVVH group ( $P=0.16$ ). The estimated unbound concentrations resulting from piperacillin continuous infusion were above the target susceptibility breakpoint (16 mg/L) for the entire dosing interval (100%  $f_{L_{MIC}}$ ) in all study patients.

In the present study, higher (but not significantly) piperacillin clearance and lower piperacillin exposure were observed in patients receiving CVVHDF compared with CVVH. In patients receiving CRRT, the use of piperacillin continuous infusion should be considered to ensure optimal exposure for less susceptible pathogens.

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### 1. Introduction

Piperacillin is a broad-spectrum  $\beta$ -lactam antibiotic commonly used to treat infections in the intensive care unit (ICU). Used in combination with the  $\beta$ -lactamase inhibitor tazobactam, the optimal effect of piperacillin is closely related to the time that the concentration of piperacillin remains above the minimum inhibitory concentration (MIC) of the pathogen [1]. Referred to as 'time-dependent killing', there is rationale for administering piperacillin

as a continuous infusion (CI) over a 24-h period in the management of critically ill patients with sepsis [2,3].

Acute kidney injury (AKI) often occurs in critically ill patients, and often requires continuous renal replacement therapy (CRRT). However, extracorporeal drug clearance during CRRT can alter antibiotic pharmacokinetics through a myriad of factors including the type of CRRT and settings applied, haemofilter, fluid replacement mode (pre- or postdilution) and the physicochemical properties of the drug itself. Piperacillin is hydrophilic, like other  $\beta$ -lactams, is moderately protein bound, and has a small molecular weight so its clearance is likely influenced by the type and dose of CRRT employed. Interestingly, there are preliminary data supporting the use of piperacillin as a 24-h CI, even in the setting of CRRT, to help improve the probability of achieving specified pharmacokinetic/pharmacodynamic (PK/PD) targets for less susceptible pathogens [4].

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However, previous work has shown that interpatient variability in drug clearance makes it difficult to define prospective dosing regimens for patients with AKI receiving concomitant piperacillin and CRRT [5,6]. To the authors' knowledge, no study to date has compared extracorporeal clearance between the two common CRRT modalities [continuous venovenous haemodiafiltration (CVVHDF) and continuous venovenous haemofiltration (CVVH)] in patients receiving piperacillin CI. Therefore, the primary aim of this study was to compare the clearance of piperacillin administered as a 24-h CI between CVVHDF and CVVH applied at equal dose. It was hypothesized that CVVHDF (combined diffusive and convective techniques) would be more efficient in removing piperacillin than CVVH (convective technique alone). The secondary aim was to assess whether piperacillin CI achieved the PK/PD target of  $100\% fT_{>MIC}$  in patients receiving CRRT.

## 2. Materials and methods

### 2.1. Study design and settings

This observational PK study was a substudy of a randomized trial comparing the efficacy of an equal dose of CVVHDF (15 mL/kg/h dialysate flow rate + 15 mL/kg/h ultrafiltrate flow rate) and CVVH (30 mL/kg/h ultrafiltrate flow rate) in a tertiary referral ICU (clinicaltrials.gov NCT 01403220, completed but as yet unpublished) [7]. Ethical approval was obtained from the local ethics committee of Nîmes (Comité de Protection des Personnes Sud Méditerranée III 2012.02.05). Written informed consent was obtained from either the patient or their nominated decision-maker.

### 2.2. Study population

Inclusion criteria for this study were:

- AKI defined according to the RIFLE criteria [8] necessitating either CVVHDF or CVVH, allocated at random in the primary study.
- Clinical indication for piperacillin-tazobactam.

Exclusion criteria were:

- Requirement of CRRT for cardiogenic pulmonary oedema, metabolic acidosis ( $\text{pH} < 7.15$ ,  $\text{HCO}_3^- < 12$  mmol/L) or hyperkalaemia  $> 6.5$  mmol/L.
- History of allergy or contraindication to piperacillin-tazobactam.

### 2.3. Continuous renal replacement therapy settings

Both CRRT techniques were performed using an Aquarius system (Nikkiso, Japan) and a polysulfone-type haemofilter with a surface area of 1.9 m<sup>2</sup> (Aquamax HF19).

The CRRT settings were:

- A 15 mL/kg/h ultrafiltrate rate + 15 mL/kg/h dialysate flow rate for CVVHDF and a 30 mL/kg/h ultrafiltrate rate for CVVH. For both techniques, fluid replacement was applied after dilution.
- The net fluid removal rate was at the physician's discretion between 0 and 200 mL/h.
- The targeted blood flow rate was aimed at providing a filtration ratio  $< 20\%$ . The filtration ratio was calculated as follows: (ultrafiltrate flow rate + net fluid removal) / blood flow rate.

### 2.4. Drug administration and sampling procedure

A loading dose of 4.5 g over 1 h followed by CI (500 mg/h) of piperacillin-tazobactam was administered intravenously as part of the patients' prescribed antimicrobial therapy. Three to seven blood samples were drawn between day 1 and day 6 of piperacillin-tazobactam therapy. Blood samples from the CRRT circuit before the haemofilter (prefilter samples) to determine total plasma piperacillin concentrations were taken at baseline (predose) and 1, 2, 4 and 8 h after the start of piperacillin-tazobactam infusion. Blood samples immediately after the haemofilter (postfilter samples) were taken 2, 4 and 8 h after the start of piperacillin-tazobactam infusion. Blood samples were placed on ice immediately, centrifuged at 3000 rpm for 10 min, then stored at  $-80^\circ\text{C}$ . Samples were transported (with a temperature log on dry ice) by a commercial courier company to the Burns Trauma and Critical Care Research Centre, University of Queensland, Australia for further analysis.

### 2.5. Data collection

Additional clinical and demographic data were collected, including Simplified Acute Physiology Score II score [9] at ICU admission, Sequential Organ Failure Assessment score [10], comorbidities and 28-day outcome. During the CRRT treatment, CVVHDF or CVVH settings were also recorded. Type of infection, microbiological cultures and MIC (if available) were collected.

### 2.6. Piperacillin assay

Total piperacillin concentrations in plasma were measured by a validated UHPLC-MS/MS method from 0.5 to 500 mg/L. Clinical samples were assayed alongside calibrators and quality controls, and met batch acceptance criteria of the US Food and Drug Administration's guidance for industry on bioanalysis (available at: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf)). Interbatch precision was  $\leq 1.9\%$  and accuracy was  $\leq 9.7\%$  at the three concentrations tested. Unbound concentrations of piperacillin were calculated from total concentrations by using a fixed 0.3 protein binding based on the results from Wong et al, which found good correlation between measured and calculated unbound concentrations ( $R^2 = 0.9892$ ,  $P < 0.0001$ ) [11].

### 2.7. Pharmacokinetic analysis

The pharmacokinetic parameters were determined using a non-compartmental approach. The area under the concentration time curve for plasma from 0 to 8 h ( $\text{AUC}_{0-8}$ ) was calculated using the linear trapezoidal rule. Total body clearance was calculated as maintenance rate divided by steady state piperacillin plasma concentration ( $C_{ss}$ ).

The clearance of piperacillin by CRRT was assessed as follows:

$$\text{Piperacillin clearance by CRRT} = (C_{\text{pre}} - C_{\text{cor,post}}) / C_{\text{cor,post}} * \text{BFR}$$

where  $C_{\text{pre}}$  is the piperacillin prehaemofilter concentration (mg/L),  $C_{\text{cor,post}}$  is the piperacillin posthaemofilter concentration corrected for postdilution (mg/L), and BFR is the blood flow rate (mL/min).

Posthaemofilter concentrations were corrected for postdilution as follows:

$$C_{\text{cor,post}} = C_{\text{post}} * (\text{BFR} - \text{PDR} - \text{FRR}) / \text{BFR}$$

where  $C_{\text{post}}$  is the measured piperacillin posthaemofilter concentration, BFR is blood flow rate (mL/min), PDR is postdilution rate (mL/min) and FRR is fluid removal rate (mL/min).

### 2.8. Pharmacodynamic analysis

A susceptibility breakpoint of 16 mg/L for piperacillin against *Pseudomonas aeruginosa* based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database [12] was used to determine the frequency of PK/PD target attainment. The PK/PD target of plasma drug concentrations (unbound) above the MIC breakpoint for the entire dosing interval ( $100\% fT_{>MIC}$ ) was considered [13].

### 2.9. Statistical analysis

Continuous data are presented as the mean (standard deviation) or median (interquartile range). Categorical data are presented as counts (%). The Shapiro–Wilk test was used to test for normality. Comparisons used the Mann–Whitney *U*-test and Student's *t*-test as appropriate.  $P < 0.05$  was considered to indicate statistical significance, and all analyses were performed using GraphPad Prism Software 6.0 (San Diego, CA, USA).

## 3. Results

### 3.1. Demographic and clinical data

Eighteen PK profiles from 12 eligible patients treated with piperacillin-tazobactam who received CRRT were analysed. The demographics, illness severity and anthropometric data of the enrolled patients are shown in Table 1. Vasopressor support was required in 16 (89%) study CRRT sessions. The pathogens identified were: *Escherichia coli* ( $n = 3$ ), *P. aeruginosa* ( $n = 1$ ), *Acinetobacter baumannii* ( $n = 1$ ), *Klebsiella pneumoniae* ( $n = 1$ ), *Enterococcus faecalis* ( $n = 1$ ) and *Serratia marcescens* ( $n = 1$ ). The range of Gram-negative MICs was 2–64 mg/L.

### 3.2. Replacement renal therapy

Five patients received alternate CVVHDF and CVVH, and one patient was sampled on two different occasions on CVVH. The CRRT settings across both CVVHDF and CVVH treatments are shown in Table 2.

### 3.3. Pharmacokinetic/pharmacodynamic analysis

The mean observed piperacillin concentration time profiles in plasma on CVVHDF and CVVH are shown in Fig. 1. Lower (but not

**Table 1**  
Demographic and anthropometric characteristics, and illness severity of 12 included patients.

Demographics	n (%) or mean (SD)
Sex: female/male	2/10
Age (years)	70 (16)
Weight (kg) at admission	77 (18)
Height (cm)	170 (12)
Body mass index (kg/m <sup>2</sup> )	26 (5)
Comorbidities	n (%)
Hypertension	7 (58%)
Chronic kidney disease	1 (8%)
COPD	4 (3%)
Child Pugh B cirrhosis	1 (8%)
Severity scores	Mean (SD)
SAPS II score at admission	55 (11)
SOFA score at admission	10 (3)
Outcome	
28-day survival	7 (58%)

COPD, chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiology score II; SOFA, Sequential Organ Failure Assessment score; SD, standard deviation.

**Table 2**  
Clinical and biological data and continuous renal replacement therapy (CRRT) parameters during CRRT sessions.

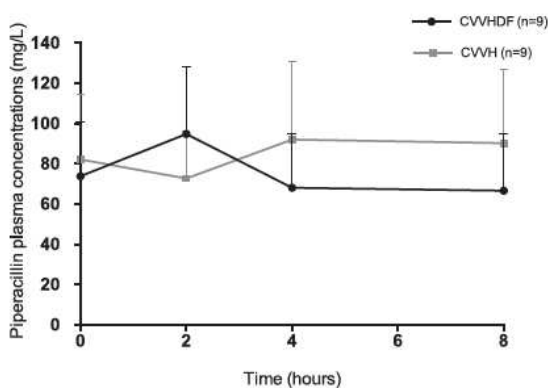
	CVVHDF (n = 9)	CVVH (n = 9)	P-value
Clinical parameters			
SOFA score on sampling day	10 (4)	10 (2)	0.94
12-h urine output (mL)	362 (465)	533 (586)	0.50
MAP (mmHg)	74.8 (14.8)	79.9 (12.9)	0.48
Biological parameters			
Albumin (g/L)	26.2 (6.3)	24 (8.6)	0.54
Creatinine ( $\mu$ mol/L)	225 (62)	256 (82)	0.38
Urea (mmol/L)	17.4 (7.9)	18.4 (7.4)	0.78
CRRT parameters			
Blood flow rate (mL/min)	203 (31)	233 (42)	0.10
Dialysate flow rate (mL/kg/h)	15.7 (2.4)	NA	NA
Ultrafiltration rate (mL/kg/h)	15.8 (3.1)	31.1 (9.2)	<b>0.0002</b>
Fraction filtration ratio (%)	10 (3)	17 (2)	<b>&lt;0.0001</b>
Filter age (h)	4.9 (6.4)	7.1 (7.5)	0.51
Transmembrane pressure (mmHg)	47 (36)	81 (27)	<b>0.04</b>
Fluid removal (mL/h)	50 (60)	85 (100)	0.38
Pharmacokinetic parameters			
Piperacillin infusion rate (mg/h)	518 (55)	500 (0)	0.33
C <sub>max</sub> (mg/L)	80.5 (27.4)	104.8 (39.2)	0.15
C <sub>ss</sub> (mg/L)	68.4 (25.8)	89.1 (35.6)	0.16
Total clearance (L/h)	7.5 (5.9–11.2)	4.7 (4.5–9.6)	0.21
AUC <sub>0–8</sub> (mg.h/L)	516 (228)	686 (314)	0.21
Clearance related to CRRT (L/h)	3.0 (2.7–3.2)	2.6 (1.9–3.0)	0.29

CVVHDF, continuous venovenous haemodiafiltration; CVVH, continuous venovenous haemofiltration; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment score; C<sub>max</sub>, maximal piperacillin concentration; C<sub>ss</sub>, steady-state piperacillin concentration; AUC<sub>0–8</sub>, area under the concentration time curve from 0 to 8 h.

The Shapiro–Wilk test was used to test for normality. Results are expressed as mean (standard deviation) or median (interquartile range) according to the normality assessment. Comparisons using Student's *t*-test or Mann–Whitney *U*-test, statistically significant if  $P < 0.05$ .

significantly) piperacillin C<sub>ss</sub> and AUC<sub>0–8</sub> were observed on CVVHDF (Table 2). Total piperacillin clearance was higher in CVVHDF without reaching statistical significance ( $P = 0.21$ ). CRRT-related clearance accounted for 40% and 55% of total piperacillin clearance in the CVVHDF and CVVH groups, respectively.

The PK/PD target of  $100\% fT_{>MIC}$  was achieved in 100% (eight of eight) patients in the CVVHDF group and 100% (eight of eight) patients in the CVVH group considering the EUCAST breakpoint of 16 mg/L against *P. aeruginosa*.



**Fig. 1.** The observed mean concentration-time profiles for 8-hour sampling interval of piperacillin in critically ill patients receiving CVVHDF or CVVH.

#### 4. Discussion

In this prospective study, the comparison of piperacillin PK across two different modalities (CVVHDF combining diffusion and convection and CVVH using convection alone) set at equal doses found that CVVHDF resulted in higher (but not significantly) piperacillin clearance and lower piperacillin exposure. In both groups, piperacillin CI achieved the PK/PD target of 100%  $f_{T-MIC}$  when considering the EUCAST *P. aeruginosa* susceptibility breakpoint of 16 mg/L in all patients, regardless of the CRRT modality applied.

Piperacillin PK in critically ill patients receiving CRRT has been studied previously [4,14–17]. However, to the best of the authors' knowledge, none of these studies have compared the effects of similar CRRT settings (i.e haemofilter, CRRT dose, postdilution mode) on PK of piperacillin administered by CI. In this study, the piperacillin clearance was higher in CVVHDF but did not reach statistical significance. One previous study compared piperacillin clearances between CVVHDF and CVVH [14]. In this study, Valtonen et al found 1.5-fold higher piperacillin clearance in CVVHDF compared with CVVH. However, the effluent rate applied in patients receiving CVVHDF (22.2 mL/kg/h and 31 mL/kg/h) was higher compared with CVVH (8.8 mL/kg/h) [14], which would have contributed to the observed difference in piperacillin clearance. In the present study, using the same haemofilter (1.9 m<sup>2</sup>) and CRRT doses (30 mL/kg/h effluent rate), higher piperacillin clearance was observed in CVVHDF compared with CVVH. These findings suggest that diffusion is an important factor influencing piperacillin clearance across the haemofilter. Moreover, as piperacillin clearance differs between groups, not only for CRRT-related clearance but also for total drug clearance itself, with a higher magnitude in the CVVHDF group, it could be hypothesized that changes in alternative piperacillin elimination pathways may also contribute to the observed difference.

Given the time-dependent activity of piperacillin, administration by CI could be useful to increase the achievement of optimal exposures in CRRT. A previous study comparing CI and bolus infusion in critically ill patients receiving CVVH showed that CI was associated with higher achievement of PK/PD targets (87.5% of patients) compared with bolus infusion (62.5% of patients) [4]. As CVVHDF leads to higher piperacillin clearance, this CRRT modality could increase the risk of piperacillin subtherapeutic concentrations if adequate piperacillin doses are not prescribed. In the present study, piperacillin CI achieved the PK/PD target of 100%  $f_{T-MIC}$  in all patients for less susceptible pathogens. However, high inter- and intra-individual PK variability was observed in the study population, supporting the concomitant use of therapeutic drug monitoring to ensure adequate piperacillin exposure in critically ill patients receiving CRRT. This would be particularly important if lower doses of piperacillin were used. These results suggest that, in daily practice, dosing adjustment may be required in critically ill patients receiving piperacillin CI, based on the nature (diffusive and convective or purely convective) of the CRRT technique applied. A reduction in the total daily dose associated with therapeutic drug monitoring may be considered while using piperacillin CI.

This study had a few limitations. Firstly, a larger sample size may have enabled the detection of statistical differences in clearance and steady state concentration between the groups. However, to the best of the authors' knowledge, this study reports data from the largest cohort of patients receiving piperacillin CI and CRRT in the literature. Secondly, despite the drug formulation containing both piperacillin ( $\beta$ -lactam antibiotic) and tazobactam ( $\beta$ -lactamase inhibitor), tazobactam concentrations were not available in this study. Thirdly, the authors could not assess mechanistically the part of piperacillin adsorbed on the haemofilter or removed across the haemofilter, or the part eliminated in urine as piperacillin concentrations into CRRT effluent and residual urine were not available in this study. Although it may be mechanistically interesting, this

difference appears to be less clinically relevant. The requirement for antimicrobial dosing adjustment depends on the total amount of drug removed during CRRT regardless of the underlying mechanism. Fourthly, sampling data were available for the first 8 h of the sampling interval alone, precluding AUC<sub>0–24</sub> being calculated. However, it is not believed that this limitation alters the findings of the study, as assumed steady state concentrations in patients receiving piperacillin CI have been studied.

#### 5. Conclusion

In this study, CVVHDF resulted in higher piperacillin clearance and lower steady state concentrations compared with CVVH. In all patients receiving CVVHDF or CVVH, piperacillin CI achieved the PK/PD target of 100%  $f_{T-MIC}$  considering a susceptible breakpoint of 16 mg/L. These data suggest that the use of piperacillin CI in patients receiving CRRT with regular therapeutic drug monitoring to ensure optimal exposure is a potentially viable modality for the treatment of less susceptible pathogens such as *P. aeruginosa*. Further data are required to test the clinical superiority of CI in patients receiving CRRT.

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## ***9. PERSPECTIVES***

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Ce travail de thèse a généré de nombreuses pistes de réflexion sur l'optimisation potentielle de la PK/PD des anti-infectieux dans la population de patients de réanimation.

Les projets élaborés dans la continuité de cette thèse ont été axés :

### **1) Sur une meilleure caractérisation des altérations induites par le sepsis sur la PK des antibiotiques notamment des aminosides et des antifongiques**

Pour cela, nous utilisons une approche transversale consistant à mener en parallèle une étude PK animale portant sur les échinocandines dans un modèle de choc septique porcin (**étude FongiPig**) et une étude PK humaine portant sur le comportement des échinocandines chez les patients en choc septique secondaire à une infection intra-abdominale compliquée (**étude EPI study**). L'étude animale comprenant un groupe septique et un groupe contrôle permettra une analyse approfondie des différents effets du sepsis et d'identifier les covariables potentiellement affectant la PK des échinocandines. L'étude humaine conduite en parallèle de l'étude animale permettra de confronter les données animales aux données humaines afin d'évaluer si le modèle animal peut permettre de prédire les effets du sepsis sur la PK des anti-infectieux chez l'humain.

### **2) Sur un meilleur usage des aminosides dans la population de patients de réanimation**

Afin d'évaluer le bon usage des aminosides, nous conduisons un essai multicentrique sur une large cohorte de patients de réanimation (1000 patients) afin de décrire les pratiques d'administration d'aminosides (**étude AMINO III**) à l'échelon international et de décrire les concentrations plasmatiques d'aminosides obtenues dans cette population.

Afin d'évaluer le risque associé à l'usage des aminosides, nous conduisons également une étude prospective monocentrique sur une cohorte de 400 patients de réanimation recevant

un traitement par aminosides afin d'identifier les facteurs potentiels de risque de néphrotoxicité (**étude AMINO IV**). Enfin, dans un travail prospectif multicentrique (étude AMINO VI), nous cherchons à redéfinir les cibles PK/PD des aminosides administrés aux doses recommandées (AFSSAPS 2011) associées à l'évolution et à la guérison clinique et microbiologique des patients. Les cibles testées (ratio C<sub>max</sub>/CMI et AUC/CMI) feront appel à deux techniques différentes de CMI. La technique de diffusion des disques classiquement utilisée et la technique d'antibiofilmogramme qui permet de quantifier la production de biofilm généré par la bactérie incriminée et qui pourrait expliquer en partie les échecs thérapeutiques malgré des concentrations cibles atteintes.

### **3) Sur la faisabilité de l'utilisation de logiciel d'optimisation PK/PD pour la prescription individualisée d'antibiotiques**

Enfin la meilleure connaissance des altérations PK liées au sepsis et la maîtrise d'outils de modélisation PK/PD a pour but *in fine* d'optimiser la prescription des antibiotiques dans cette population à risque de doses inappropriées que représente la population de réanimation. Pour cela, des logiciels de prescription optimisée et individualisée ont été développés (logiciel DoseMe, BestDose, ODDS). Toutefois, ces logiciels n'ont pas été validés dans des cohortes de patients de réanimation. Nous élaborons donc un projet d'optimisation de la prescription d'aminosides au lit du malade à l'aide d'un logiciel de prescription individualisée : BestDose dont le fonctionnement repose sur une analyse de population proche de celle réalisée avec le logiciel Pmetrics (**projet AminoBestDose**).

## *10. CONCLUSION*

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La gravité des patients, le sepsis et les défaillances d'organes nécessitant parfois de recourir à l'EER ainsi que l'incidence élevée de germes de sensibilité diminuée font de la réanimation un véritable défi à l'usage optimal des antibiotiques. Dans ce contexte d'émergence de résistance bactérienne menaçant nos sociétés, une bonne connaissance de la pharmacocinétique des antibiotiques pourrait permettre d'optimiser leur utilisation. Les posologies conventionnelles recommandées sont la plupart du temps inadaptées aux patients de réanimation. Les logiciels PK/PD développés ces dernières années et permettant de réaliser une analyse pharmaco-statistique plus complexe ont permis de mieux comprendre les adaptations posologiques requises dans cette population. Une augmentation des posologies est souvent nécessaire à la phase initiale du sepsis. Le recours à l'EER va influencer la PK des antibiotiques avec un degré variable selon les propriétés physico-chimiques de l'antibiotique plus que selon le type d'EER appliqué. Du fait d'une très grande variabilité inter-individuelle, le monitoring des concentrations plasmatiques d'antibiotiques apparaît indispensable pour leur utilisation optimale. Malheureusement, le dosage en routine des antibiotiques reste peu développé. La prescription individualisée faisant appel à des logiciels de modélisation PK/PD pourrait permettre à l'avenir d'optimiser l'utilisation des antibiotiques tant en terme d'efficacité que de toxicité tout en limitant l'émergence de résistance.

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## Résumé

Le bon usage des antibiotiques en réanimation est un véritable défi. Le sepsis et l'épuration extra-rénale peuvent modifier le comportement des anti-infectieux exposant le patient au risque de sous ou de surdosage. Une meilleure compréhension des altérations liées au sepsis et aux défaillances d'organe permet d'adapter les posologies d'antibiotiques. L'augmentation des posologies d'antibiotiques est nécessaire à la phase initiale du sepsis en raison d'un volume de distribution augmenté. Les adaptations posologiques vont ensuite dépendre des propriétés physico-chimiques de l'anti-infectieux plus que du type d'épuration extra-rénale appliquée. La modélisation pharmacocinétique de population couplée à des simulations de Monte Carlo est une approche pharmaco-statistique élaborée permettant de définir pour une population spécifique les paramètres influençant la PK de l'antibiotique et de prendre en considération la variabilité inter-individuelle. Cette analyse permet également de tester différents schémas posologiques pour un antibiotique donné afin de déterminer la posologie optimale en fonction de différentes fonctions d'organe et selon la susceptibilité des germes traités. La prescription individualisée faisant appel à des logiciels de modélisation PK/PD pourrait permettre à l'avenir d'optimiser l'utilisation des antibiotiques tant en terme d'efficacité que de toxicité tout en limitant l'émergence de résistance.

## Abstract

Prescribing antibiotics in an appropriate way is a massive challenge for the intensivists. Sepsis and renal replacement therapy may alter antibiotics pharmacokinetics exposing critically ill patients to under or overdosing. A better understanding of sepsis and organ failure related alterations could help optimizing antibiotic drug dosing. Increased dosing regimens are often necessary at the early phase of sepsis due to increased volume of distribution. Dosing adjustment will then depend on the physicochemical properties of the anti-infective agent rather than renal replacement therapy modalities. A population pharmacokinetic analysis coupled to Monte Carlo simulations consists in a pharmaco-statistic approach aiming to identify covariates influencing antibiotics PK and to consider inter-individual variability. This analysis allows testing different dosing scenarios to determine the optimal dosing regimen according to different levels of organ dysfunction and according to pathogen susceptibility. Individual drug dosing optimisation, using PK/PD modelling software could improve antibiotic efficacy while limiting antibiotic-related toxicity and antimicrobial resistance.