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Aminoglycosides in Critically Ill Septic Patients With Acute Kidney Injury Receiving Continuous Renal Replacement Therapy: A Multicenter, Observational Study

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ABSTRACT

Purpose: Data on aminoglycoside stewardship in critically ill septic patients with acute kidney injury (AKI) needing continuous renal replacement therapy (CRRT) are scarce. The objectives of the study were to determine, during CRRT, the time window with low likelihood for safe reinjection and the proportion of inappropriate reinjection.

Methods: A post hoc observational analysis of a multicenter randomized trial comparing the risk of hemodialysis catheter infection with ethanol lock vs placebo in critically ill patients with AKI was conducted. Eligible patients were adults in intensive care units from 6 French hospitals. Any patient with AKI needing CRRT and receiving an antimicrobial therapy for a septic episode occurring before (≤ 24 hours) or during CRRT was included. The aminoglycoside orders were left to the physicians' discretion, but high dose once daily was the schedule of aminoglycoside administration.

Findings: A total of 145 septic episodes treated by aminoglycosides were analyzed in patients receiving CRRT. A mean (SD) of 1.6 (0.8) amikacin and 1.8 (1.2) gentamicin administrations per patient were observed. During CRRT, C_{\max} was 17.3 mg/L (interquartile range, 13.2-22.5 mg/L) for gentamicin and 50 mg/L (interquartile range, 43.7-76.6 mg/L) for amikacin. The plasma drug concentration at 24 hours (C_{H24})

was 2.3 mg/L (interquartile range, 1.6-3.2 mg/L) for gentamicin and 9.3 (interquartile range, 6.6-12.0 mg/L) for amikacin. Sixty-five C_{\min} dosages remained above the reinjection threshold. Inappropriate reinjection was observed in 11 of 65 episodes (17%). Inappropriate reinjection (defined by, at the reinjection time, C_{\min} dosages above the threshold; ie, $C_{\min} > 2$ mg/L for gentamicin and > 5 mg/L for amikacin) was observed in 17% of analyzed episodes. Most patients did not need reinjection until approximately ≥ 30 hours after their initial administration.

Implications: During CRRT, as indicated by the C_{H24} value, which was higher than the recommended threshold, the interval to obtain a C_{\min} low enough to allow for redosing aminoglycosides is significantly longer than 24 hours. This interval is not always respected and leads to an of inappropriate reinjection rate of 17%. ClinicalTrials.gov identifier: ISRCTNCT00875069. (*Clin Ther.* 2021;XX:XXX-XXX) © 2021 Elsevier HS Journals, Inc. (*Clin Ther.* 2021;000:1-9.) © 2021 Published by Elsevier Inc.

Keywords: Acute kidney injury, aminoglycosides, continuous renal replacement therapy, critical care, sepsis.

INTRODUCTION

Ten percent of intensive care unit (ICU) patients developing acute kidney injury (AKI) require renal replacement therapy (RRT).¹ Three-quarters of these patients are treated by continuous RRT (CRRT).² The role of aminoglycosides in the occurrence of AKI in ICU patients with shock has been controverted,³ but ICU physicians still use aminoglycosides in sepsis, including in patients with AKI.⁴⁻⁶ A decade ago, aminoglycoside administration entered the era of high dose once daily (HDOD).⁴ This HDOD regimen is without nephrotoxic or ototoxic risk in patients with reduced glomerular filtration rate. In the group of patients needing CRRT, and especially in those with septic-induced AKI, data on aminoglycoside pharmacokinetic characteristics are scarce. The previous dosing recommendations (ie, 3 mg/kg of gentamicin and 10 mg/kg of amikacin⁷) are no longer adapted to the modern standards of C_{max}/MIC . Assuming that MICs may be at the upper epidemiologic cutoff in ICU patients, higher doses should be tailored to the new objectives. Most previous studies have been conducted in a limited sample of patients in quasi experimental conditions and with lower doses than currently recommended.⁸⁻¹⁰ It is important to provide data exemplifying the real-life and modern management of aminoglycosides because the sole pharmacokinetic/pharmacodynamic assessment, as reported in previous studies, cannot account for the complexity of physicians' decisions in patients with unstable conditions. By assessing routine aminoglycoside pharmacokinetic characteristics in patients receiving RRT, we aimed to determine the time window with low likelihood for safe reinjection and the proportion of inappropriate reinjection.

MATERIALS AND METHODS

Study Design and Patients

This study is a post hoc analysis of a randomized, double-blind, placebo-controlled trial entitled Ethanol Lock and Risk of Hemodialysis Catheter Infection in Critically Ill Patients (ELVIS).¹¹ Only patients in 6 of 16 ICUs (5 university hospitals and 1 general hospital) were included in this ancillary study. The study protocol was approved by the Sud-Est 1 ethics

committee in France. Written informed consent was obtained from the patients or next of kin before inclusion.

In the ELVIS study, eligible patients were adults (>18 years of age) in ICUs who required insertion of a dialysis catheter for RRT. Exclusion criteria were known ethanol intolerance and pregnancy.

In the present study, only patients receiving CRRT were included. Additional inclusion criteria consisted of any patient receiving antibiotic treatment for a septic episode. To meet the inclusion criteria, patients had to have been exposed to an antibiotic for ≤ 24 hours before (whether the patient had been already admitted to the ICU or not) or after (during their ICU stay) CRRT was initiated. All episodes that needed antibiotic treatment stopped at the ICU admission and all antibiotic treatment that lasted >72 hours before CRRT were excluded.

Interventions

In the ELVIS study, no other intervention than dialysis catheter lock (which was managed differently according to the study group) was controlled. If CRRT administration was not controlled, procedures were almost identical in each ICU. The main characteristics of renal support modalities are reported in the [Table 1](#).

The antibiotic orders were left to the physicians' discretion. However, the HDOD regimen was used for aminoglycoside administration. Daily amikacin and gentamicin doses were 20 to 30 mg/kg and 5 to 10 mg/kg, respectively.

Traditionally, a monitoring of plasma aminoglycoside concentrations was used. The concentrations were determined at the pharmacology department of each hospital by using a validated immunoassay method (QMS Amikacin Assay [Thermo Fisher Scientific, Waltham, Massachusetts] on an Olympus AU5400 [Beckman Coulter, Brea, California]). All serum aminoglycoside concentrations were returned to the physician in a range of 1 to 6 hours according to the different centers. Amikacin or gentamicin levels measured at 1 hour (C_{max}) after the onset of perfusion (ie, 30 mn after the end of perfusion) and within 2 hours before the next injection or at 24 hours in case of no reinjection (C_{min}). The different centers reported to fit with the same C_{max} and C_{min} objectives: C_{max} from 20 to 30 mg/L for gentamicin and 40 to 80 mg/L for amikacin and C_{min} from 0.5 to 2.0 mg/L for gentamicin and from 2.5 to 5.0 mg/L for amikacin.

Table 1. Characteristics of the renal support modalities.		
Characteristic	CRRT (n = 145)*	
	CVVHF (n = 108)	CVVHDF (n = 43)
Blood flow, mean (SD), mL/min	250 (40)	239 (45)
Dialysate flow, median (IQR) [†]	No	1273 (907)
Prehemofilter dilution flow, mean (SD), mL/h	1286 (565)	801 (938)
Posthemofilter dilution flow, mean (SD), mL/h	2015 (625)	705 (1017) [‡]
Fluid removal, mean (SD), mL/h	65 (87)	NA

CCRT = continuous renal replacement therapy; CVVHDF = continuous veno-venous hemodiafiltration; CVVHF = continuous veno-venous hemofiltration; IQR = interquartile range; NA = not available.

*In 6 septic episodes, patients received both CVVHDF and CVH.

[†] Reported in milliliters per hour during CRRT and milliliters per minute during intermittent hemodialysis.

[‡] No posthemofilter dilution in a single center (n = 18 septic episodes).

Definitions

Sepsis was defined by any suspected infection that required an antimicrobial therapy according to bedside physicians. Septic episodes were defined as several distinct sepsis episodes during a patient's ICU stay. Each distinct septic episode could be the subject of a new inclusion because the analyzed event was an episode of antibiotic-treated sepsis. In patients receiving both CRRT and intermittent haemodialysis (IH) a first episode was analyzed in this study while the patients received CRRT, and a subsequent nosocomial septic episode while the same patient received IH was included in another study. Infection site was defined according to aminoglycoside tissue penetration¹²: poor (cerebrospinal fluid, joint), middle (alveolar fluid, skin, and soft tissue), or good (abdominal, urinary tract, blood).

Main Outcomes

Each septic episode has been analyzed. Aminoglycoside pharmacokinetic characteristics during CRRT was the first outcome (goal 1) (Figure 1). C_{max} , C_{min} (defined by a dosage of aminoglycoside concentration within 2 hours before the next injection or at 24 hours in case of no reinjection), C_{H24} (defined by a dosage of aminoglycoside concentration at 24 hours of their administration), $C_{intermediate}$ (defined by a dosage of aminoglycoside concentrations between C_{max} and C_{min}), number of administrations, length of AG treatment, and number of AG injections (according to C_{mzx} and C_{min}) matching with pharmacodynamic recommendations (amikacin C_{max} of 40–80 mg/L, gentamicin C_{max} of 20–30 mg/L; amikacin C_{min} <5 mg/L and gentamicin C_{min} <2 mg/L) were assessed.

After having excluded patients in whom no C_{min} monitoring was performed because of no scheduled second reinjection, we assessed 2 other outcomes (goal 2) (Figure 1). After the first injection, an inappropriate reinjection corresponded to a new subsequent injection preceded by an aminoglycoside C_{min} dosage above the toxic C_{min} threshold (ie, C_{min} >2 mg/L for gentamicin and >5 mg/L for amikacin). Time window with low likelihood for successful reinjection corresponded to the time window until the median (interquartile range) of the aminoglycoside dosage remained in large part above the recommended threshold for toxic C_{min} . A second and more restrictive interpretation of this time window is presented in which this time window is defined by the interquartile range of the aminoglycoside dosage strictly remaining above the toxic C_{min} .

Statistical Analysis

Results are expressed as mean (SD) or median (interquartile range [IQR]). Continuous variables were compared using 2 tests: the Mann-Whitney-Wilcoxon test for independent variables and the Wilcoxon signed-rank test for the matched paired series. Categorical variables were compared using the Fisher exact test. All *P* values and *C*_{is} were two-tailed. *P* < 0.05 was considered statistically significant. All data were analyzed and processed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

From the ELVIS study (critically ill patients with AKI needing RRT), only 303 patients developed

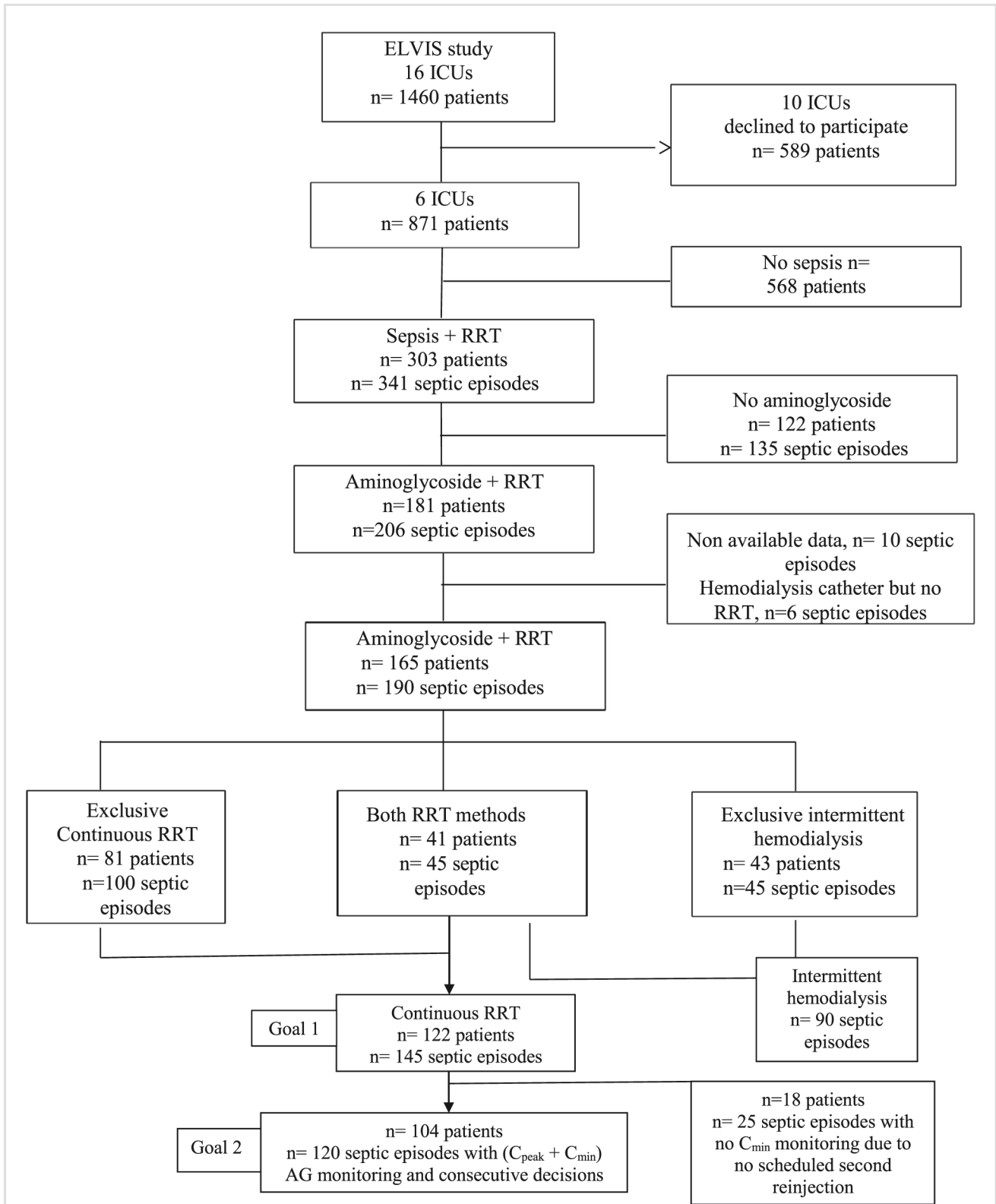


Figure 1. Aminelvis study flowchart. CCRT = continuous renal replacement therapy; ELVIS = Ethanol Lock and Risk of Hemodialysis Catheter Infection in Critically Ill Patients; ICU = intensive care unit; RRT = renal replacement therapy.

341 septic episodes (Figure 1). Aminoglycosides were administered in 206 septic episodes (60%). All the aminoglycosides were administered in the 24 hours preceding or on the first hours after ICU admission. Among the 206 septic episodes with aminoglycoside and RRT, 145 septic episodes corresponding to 122 patients receiving CRRT (45 episodes with a combination of CRRT and intermittent hemodialysis) defined the study population (Figure 1). The patients with severe disease (Simplified Acute Physiology II score of 79 [18] and Sequential Organ Failure Assessment score of 15.6 [4.5]) were more often men (sex ratio, 2.15), had a body mass index of 29.4 (7.8), had 0.5 (0.8) comorbidities (21 with diabetes, 21 with chronic kidney disease, 4 with a history of renal transplantation, 8 with liver disease, and 2 with solitary kidney).

Amikacin ($n = 96$) and gentamicin ($n = 49$) doses in patients receiving CRRT were 20.2 (6.6) mg/kg and 6.0 (1.95) mg/kg without difference, with doses used in the whole population needing RRT (20.2 [6.2] mg/kg, $P = 0.98$ and 5.7 [2.2] mg/kg, $P = 0.7$, respectively). During a septic episode, only 1 dose was administered in 44% of patients receiving amikacin and 49% receiving gentamicin. The number of aminoglycoside administrations for 1 septic episode was similar between the amikacin (2.2 [1.4]) and gentamicin (2.2 [1.5]) groups ($P = 0.87$). No difference was observed for the interval between 2 doses (1.5 [0.6] days for the amikacin group vs 1.5 [0.9] days for the gentamicin group; $P = 0.82$), and the total duration of AG treatment was 2 (1.4) days for the amikacin group and 2 (1.7) days for the gentamicin group. The renal support modalities are summarized in the Table.

Among the 145 episodes, after exclusion of 25 episodes in which no C_{\min} monitoring was performed because of no scheduled second reinjection, 120 comprehensive ($C_{\max} + C_{\min}$) aminoglycoside monitoring and consecutive decisions were analyzed. Gentamicin and amikacin C_{\max} values were 17.3 mg/L (IQR, 13.2–22.5 mg/L) and 50 mg/L (IQR, 43.7–76.6 mg/L), respectively. Figure 2 presents the C_{\max} values of gentamicin (Figure 2A) and amikacin (Figure 2B). The C_{H24} values for gentamicin and amikacin were 2.3 mg/L (IQR, 1.6–3.2 mg/L) and 9.3 mg/L (IQR, 6.6–12 mg/L), respectively. Sixty-five C_{\min} dosages remained above the reinjection threshold. Inappropriate reinjection was observed in 11 of 65 episodes (17%).

Figure 3 shows the distribution of $C_{\text{intermediate}}$ and C_{\min} monitoring results according to the interval after AG administration in the 120 episodes during which aminoglycoside concentration monitoring was performed. According to these pharmacokinetic characteristics, the time window with low likelihood for successful reinjection was, for most aminoglycoside administrations, 30 hours for amikacin and 32 hours for gentamicin from their initial administration. In a more restrictive interpretation (see Methods), the time window would be 16 to 20 hours for amikacin and 21 to 23 hours for gentamicin.

DISCUSSION

To our knowledge, this study is the first to report a multicenter description of real-life and modern management of aminoglycoside administration during CRRT in critically ill septic patients. In such patients, target attainment for aminoglycoside is tricky.¹³ An important individual V_d variability explained by a highly variable hemodynamic, inflammatory state, and fluid expansion is observed.¹⁴ Moreover, the k_e can be increased (therefore resulting in concentrations of aminoglycoside lower than MIC¹⁵) or decreased in the case of altered renal clearance or cirrhosis.¹⁶

Allowing for limitations attributable to the absence of standardization of pharmacokinetic assessment, this study might indicate that during CRRT the time window for low likelihood of successful reinjection was, for most aminoglycoside administrations, 30 hours for amikacin and 32 hours for gentamicin from their initial administration, which limits the number of successful redosings. Rarely, some patients exhibit earlier aminoglycoside elimination, with a time window of 16 to 20 hours for amikacin and 21 to 23 hours for gentamicin.

During CRRT, aminoglycoside clearance is dependent mainly on the membrane adsorption characteristics, the ultrafiltration rate, and CRRT modalities (continuous hemofiltration, continuous hemodialysis, or continuous hemodiafiltration).^{7,11-12,17} Determining the appropriate dosing interval remains therefore a difficult task (18–60 hours).¹⁷ In a recent single-center study by Roger et al,⁸ an amikacin dose of 25 mg/kg every 48 hours was optimal in critically ill patients undergoing continuous hemodialysis or continuous hemodiafiltration to achieve both pharmacokinetic/pharmacodynamic targets and limitation of toxicity. Like Taccone et al,⁹ who reported a shorter

2a Gentamicin (n=39)

2b Amikacin (n=81)

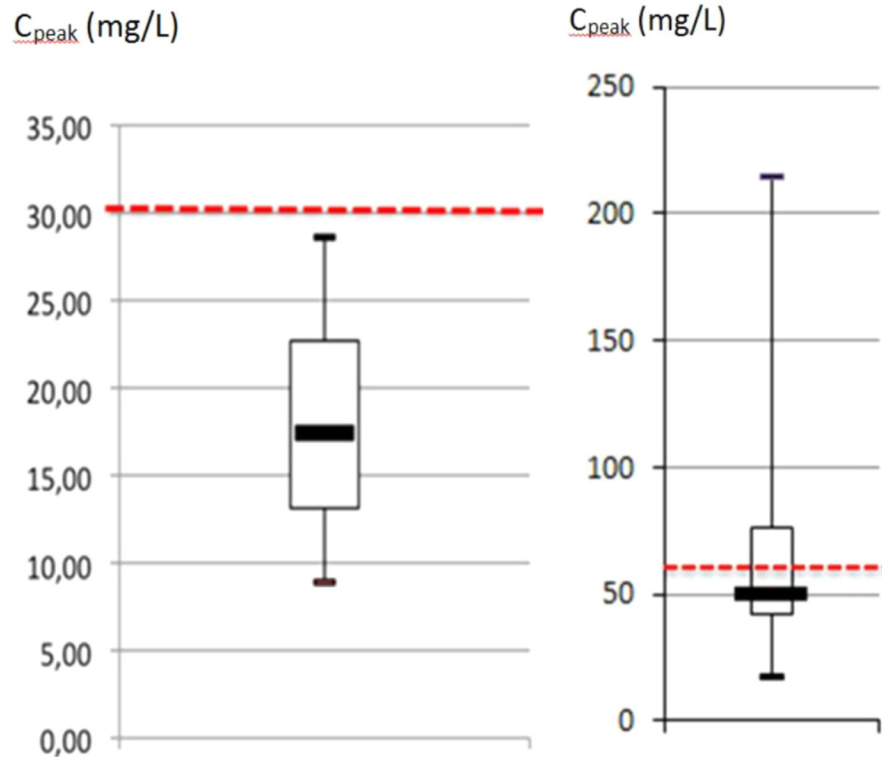


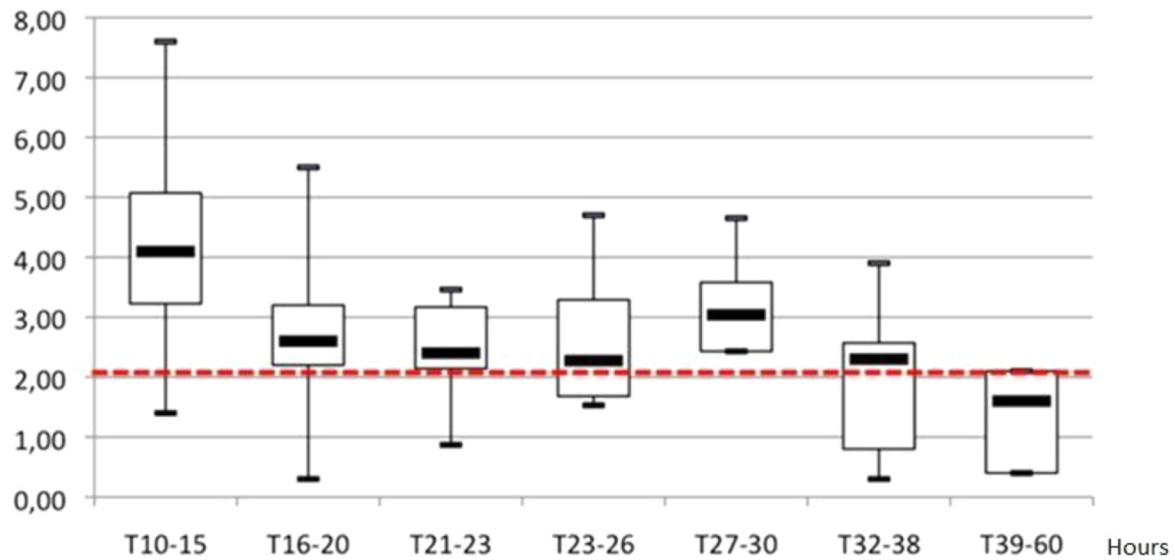
Figure 2. Aminoglycoside C_{max} monitoring in patients receiving continuous renal replacement therapy. The red dotted line corresponds to the recommended aminoglycoside C_{max} . Limits of the bins correspond to first and third percentiles of the interquartile range; black bar, median, lower and upper limits, minimal and maximal values.

median time to achieve a trough concentration of <5 mg/L in patients undergoing continuous hemodiafiltration (36 hours) with a 25-mg/kg amikacin dose,⁹ we found that a 20-mg/kg amikacin dose enabled a shorter time of reinjection (30 hours). Several authors found that conventional recommendations should be customized for patients presenting with severe sepsis or septic shock to avoid suboptimal dosing.^{7,10,12,17,18} Altogether, the results of our study as well as those of Roger et al⁸ and Taccone et al⁹ indicate that the higher the pharmacodynamic target, the higher the aminoglycoside dose and the longer the interval between 2 aminoglycoside administrations (with an interval of 30–48 hours, depending on the loading dose). The same conclusions can be drawn from our data regarding gentamicin.

Our study has some limitations. This study was not a standardized, prospective study, which explains loss to follow-up or incomplete data. We cannot eliminate a selection bias in favor of the patients receiving the best care. Moreover, the absence of systematic and identical pharmacokinetic assessment of aminoglycoside concentrations for each patient provides data of weaker evidence. In addition, this study has insufficient power to explore how variability in renal support modalities or severity of septic shock (which could modify the distribution volume accordingly) can affect the period for successful reinjection. The significant intraepisode variability observed in Figure 3 highlights the need for therapeutic drug monitoring. Finally, at the time of the study, French guidelines recommend redosing only when

a. Gentamicin (n=39)

$C_{intermediate}$ and C_{min}



b. Amikacin (n=81)

$C_{intermediate}$ and C_{min}

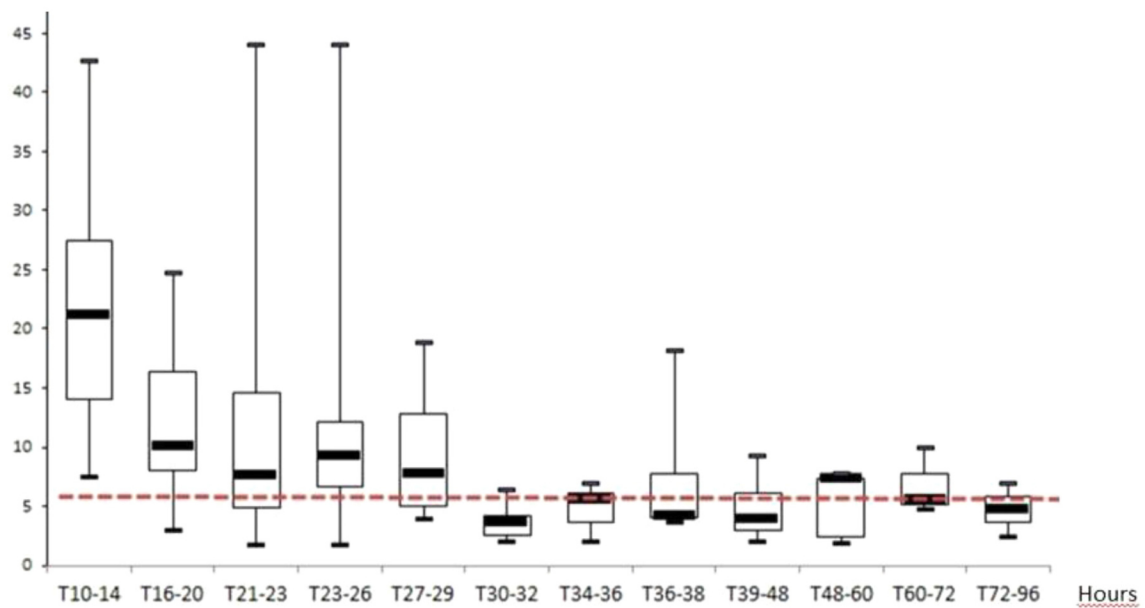


Figure 3. Aminoglycoside $C_{intermediate}$ (dosage of aminoglycoside concentrations between C_{max} and C_{min}) and C_{min} monitoring in patients receiving continuous renal replacement therapy, according to time since their administration. If several reinjections occurred, $C_{intermediate}$ corresponds to the concentration between C_{max} and C_{min} , assuming that C_{min} is the concentration obtained in the window of 2 hours before the reinjection. If no reinjection occurred, C_{min} corresponds to C_{H24} (plasma drug concentration at 24 hours), $C_{intermediate}$ corresponds to concentrations obtained before 24 hours.

aminoglycoside trough concentrations are <2.5 mg/L for gentamicin and 5 mg/L for amikacin. Trough targets to define aminoglycoside-related renal toxic effects changed in France (0.5 mg/L for gentamicin and 2.5 mg/L for amikacin) because even this choice remains questionable. For continuous hemodialysis, despite their potential impact on the pharmacokinetic characteristics of aminoglycoside, the exact amount of ultrafiltrate or dialysate flow rate in milliliters per kilogram per hour could not be reported because the patient weight was not systematically recorded.

CONCLUSIONS

In conclusion, in patients with sepsis-associated AKI receiving CRRT, the appropriate interval for redosing aminoglycosides depends on the initial dosage and is significantly longer than 24 hours, limiting further reinjection. An individualized aminoglycoside pharmacokinetic follow-up remains essential; however, such follow-up is not always performed, which may lead to a significant rate of inappropriate reinjection.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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