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# Aminoglycosides in Critically Ill Septic Patients With Acute Kidney Injury Receiving Intermittent Hemodialysis: 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 intermittent hemodialysis (IH) are scarce. The first objective of the study was to evaluate whether aminoglycoside administration occurs before vs after IH in the real-life management of critically ill septic patients with AKI needing IH. The second objective was to assess the delay in achieving a potential reinjection window for a second dose of aminoglycoside, which should be obtained with a postdialysis vs predialysis regimen.

**Methods:** A post hoc observational analysis of a multicenter randomized trial of critically ill patients with AKI needing renal replacement therapy was conducted. Inclusion criteria consisted of any patients receiving IH for AKI during an antimicrobial therapy for a septic episode.

**Findings:** Among 206 of 341 septic patients (60%) receiving aminoglycosides, 90 underwent IH (46 with previous continuous renal replacement therapy and 44 without). Amikacin and gentamicin were administered for a mean (SD) of 2.2 (1.5) and 2.5 (2.1) days with mean (SD) doses of 20.6 (6.6) and 5.4 (2.5) mg/kg, respectively. In the 44 patients undergoing exclusive IH, aminoglycosides were administered in a predialysis in 53% of episodes versus 35% in a postdialysis schedule. The first  $C_{min}$  target was obtained earlier with

a predialysis vs postdialysis schedule (33.9 [14.2] hours vs 50.9 [12.2] hours,  $P = 0.009$ ).

**Implications:** Despite being less frequently used than a predialysis schedule, the postdialysis administration of aminoglycosides remains a regular practice in the intensive care unit. A predialysis schedule of administration in IH reduces the interval time to tolerable aminoglycoside redosing. (*Clin Ther.* 2021;000:1–7.) © 2021 Elsevier Inc.

**Keywords:** acute kidney injury, aminoglycosides, critical care, intermittent haemodialysis, renal replacement therapy, sepsis.

## INTRODUCTION

Acute kidney injury (AKI) occurs in 35% to 50% of patients in the 48 hours of intensive care unit (ICU) admission, with 10% of these patients requiring renal replacement therapy (RRT).<sup>1</sup> Intermittent hemodialysis (IH) represents one-quarter of the chosen RRT modality.<sup>2</sup>

A decade ago, the treatment of sepsis with aminoglycosides entered the high-dose once-daily

(HDOD) era<sup>3</sup> (ie, 20–25 mg/kg of amikacin and 7 mg/kg of gentamicin). Despite aminoglycosides-associated nephrotoxicity, the role of aminoglycosides in the occurrence of AKI in ICU patients with shock has been controversial.<sup>4</sup> ICU physicians are thus not discouraged to use them in this context.<sup>3</sup>

Historically, when lower doses were recommended, aminoglycosides were administered just at the end of the IH session<sup>5–7</sup> as recommended by the manufacturer.<sup>8</sup> However, peak concentrations achieved by low doses did not achieve the desired  $C_{\max}$ :MIC ratios of 10:1 in most patients, especially in case of increased  $V_d$  from fluid overload or sepsis.<sup>9</sup> On the basis of the assumption that both ototoxic and nephrotoxic risks depend on the AUC<sup>10,11</sup> and that aminoglycoside efficacy depends on  $C_{\max}$ /MIC, Matsuo et al<sup>12</sup> were the first to propose a predialysis and increased dose of aminoglycosides,<sup>12</sup> followed by other investigators.<sup>9,13–15</sup> This way intermittent dialysis could remove enough of aminoglycosides so that the total drug exposure of a higher dose remained similar to that achieved by a lower dose administered after a postdialysis regimen. For example, a 6-mg/kg predialysis dose achieved higher mean (SD) peaks than a 1.7-mg/kg postdialysis dose (31.0 [10.9] vs 8.8 [3.1] kg/L), with only a moderately increased mean (SD) AUC (190.8 [65] vs 135.0 [42.2] mg/h/L).<sup>15</sup>

Other authors question the benefit-risk balance of this new regimen; they suggest, based on animal models, that time above the MIC, which may be higher with the postdialysis regimen than with the predialysis one, remains the most reliable pharmacodynamic parameter of clinical efficacy.<sup>16</sup> In an *in vitro* model of OXA-48–producing *Klebsiella pneumoniae*, the postdialysis regimen of amikacin was associated with the lowest enrichment of resistant subpopulations.<sup>17</sup>

Facing these conflicting views, to what extent the predialysis versus postdialysis schedules are now implemented in ICUs remains unknown. Moreover, how far a predialysis regimen, in removing enough of aminoglycosides, may allow an earlier aminoglycoside reinjection has not been described. The first objective of the study was to evaluate whether aminoglycoside administration occurs before versus after IH in the real-life management of critically ill septic patients with AKI needing IH. The second objective was to assess the delay in achieving a potential reinjection window for a second dose of aminoglycosides, which should be obtained with a postdialysis vs predialysis regimen.

## MATERIAL AND METHODS

### Study Design and Patients

This study is a post hoc analysis of a multicenter ( $n = 16$  centers), randomized, controlled study<sup>18</sup> of adults requiring RRT for AKI (Kidney Disease Improving Global Outcomes 3). In the present study, only 6 of the 16 centers accepted to participate. Only patients who presented with septic episodes needing antibiotics were eligible. To specifically meet the inclusion criteria, the time window of antibiotic exposure was  $\leq 24$  hours before first RRT session (some antibiotic therapy could be initiated just before ICU admission) or after the first RRT session during their ICU stay. All episodes of antibiotic treatment stopped at the ICU admission were excluded as were patients with antibiotic treatment initiated more than 72 hours before the first RRT session. The study protocol was approved by the Sud-Est 1 Ethics Committee of France. Written informed consent was obtained from the patients or next of kin before inclusion.

### Interventions

In the initial study, no other intervention than dialysis catheter lock was controlled.<sup>18</sup> The modality (continuous RRT [CRRT] or IH) and timing of IH were left to the physicians' discretion as were antibiotic orders. Each episode of antibiotic treatment was screened, and factors associated with the decision of adding aminoglycosides or not to the empirical antimicrobial therapy were assessed via a closed questionnaire by physicians managing the patient. The HDOD regimen was used.

Monitoring of plasma aminoglycoside concentrations was left to the physician's discretion. All serum aminoglycoside concentrations were returned to the physician in a range of 1 to 6 hours according to the different centers. The different centers reported the same  $C_{\max}$  (20–40 mg/L for gentamicin and 40–80 mg/L for amikacin) and  $C_{\min}$  objectives (0.5–2 mg/L for gentamicin and 2.5–5 mg/L for amikacin). The pharmacokinetic samples were determined at the pharmacology departments 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]).

### Definitions

Sepsis was defined by a systemic inflammatory response syndrome and a suspected source of infection

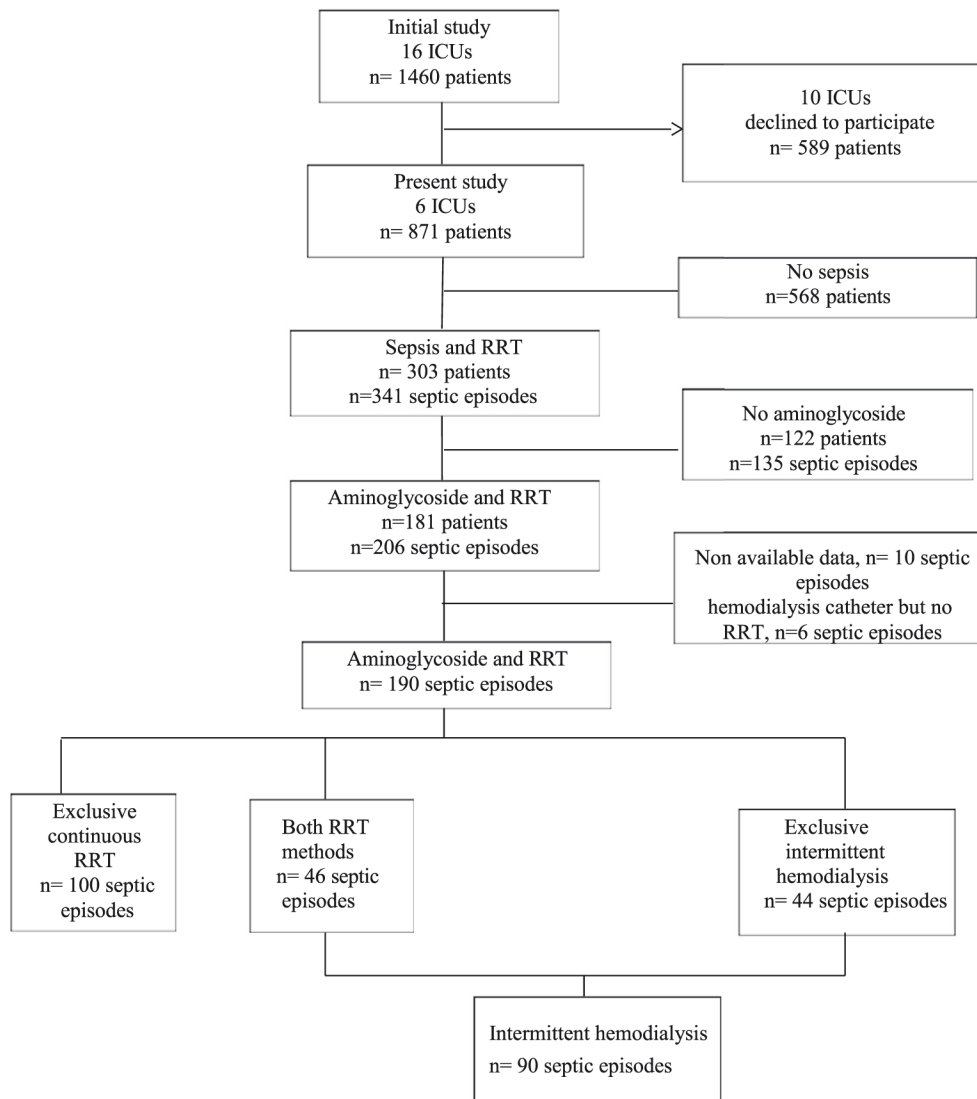


Figure. Study flow chart. ICU = intensive care unit; RRT = renal replacement therapy.

requiring an antimicrobial therapy according to bedside physicians.<sup>19</sup> When a patient developed several distinct sepsis episodes and provided a washout period (without antibiotic) occurred between them, this was considered several different septic episodes, each being the object of a new inclusion, because the analyzed event was an episode of antibiotic-treated sepsis.

Infection site according to aminoglycoside tissue penetration was defined as follows<sup>20</sup>: poor (cerebrospinal fluid and joint), middle (alveolar fluid, skin, or soft tissue), or good (abdominal, urinary tract, or blood). Successful reinjection corresponded to a new subsequent injection (after the first injection)

preceded by an aminoglycoside  $C_{min}$  dosage under the recommended target. For predialysis vs postdialysis aminoglycoside administration, an arbitrary threshold of 8 hours was selected to differentiate predialysis (hour 8 to dialysis) from postdialysis (dialysis to  $\geq 16$  hours) administration.

## Outcomes

For each septic episode, the incidence of predialysis versus postdialysis aminoglycoside administration was assessed. Aminoglycoside dosing was homogeneous among the different centers.  $C_{max}$ ,  $C_{min}$ ,  $C_{intermediate}$  (defined by a dosage of aminoglycoside concentrations



**Table I. Aminoglycoside administration and pharmacokinetic parameters.**

Variable	Amikacin	Gentamicin	<i>P</i>
<b>Administration*</b>			
No. of episodes	57	33	
No. of doses, mean (SD)	20.6 (6.6)	5.4 (2.5)	NA
Episodes with only 1 dose, %	37	43	0.29
No. of dosing days, mean (SD)	2.5 (1.6)	2.7 (2.1)	0.61
Interval between 2 doses, mean (SD), d	1.7 (1.0)	1.7 (1.1)	0.80
<b>Pharmacokinetic parameters†</b>			
No. of episodes	27	17	
$C_{\max}$ , mean (SD)‡			
Before dialysis	67.6 (28.6) (n = 19)	21.6 (3.5) (n = 4)	NA
After dialysis	26.0 (7.3) (n = 6)	19.1 (9.7) (n = 10)	
$C_{\min}$ , mean (SD)‡	3.7 (2.4)	2.0 (0.8)	NA

NA = not applicable.

\*The aminoglycoside administration characteristics (n = 90) that are reported all correspond to the period of intermittent hemodialysis, including septic episodes for which patients received continuous renal replacement therapy first and then intermittent hemodialysis (n = 46).

†Pharmacokinetic parameters are reported in septic episodes during which intermittent hemodialysis was the only renal replacement modality.

‡ $C_{\max}$  and  $C_{\min}$  were only reported in septic episodes in which patients received aminoglycosides before or after intermittent hemodialysis. Aminoglycoside  $C_{\max}$  and  $C_{\min}$  during hemodialysis were not reported (n = 2 for amikacin and 3 for gentamicin).

between  $C_{\max}$  and  $C_{\min}$ ) were assessed: amikacin or gentamicin levels were measured 1 hour ( $C_{\max}$ ) after the onset of a 30-minute perfusion and within 2 hours before the next injection or at 24 hours in case of no reinjection ( $C_{\min}$ ). The number of administrations, length of aminoglycoside treatment, and number of aminoglycoside injections (according to  $C_{\max}$  and  $C_{\min}$ ) matching with pharmacodynamic recommendations (amikacin:  $C_{\max}$  of 40–80 mg/L and  $C_{\min}$  <5 mg/L; gentamicin:  $C_{\max}$  of 20–30 mg/L and  $C_{\min}$  <2 mg/L) were assessed.

### Statistical Analysis

Results are expressed as median (interquartile range). 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 CIs were 2-tailed.

### RESULTS

Eligible critically ill patients (n = 303) developed 341 septic episodes (Figure). Aminoglycosides, including gentamicin (n = 71), amikacin (n = 145), or both (n = 10), were administered in 206 septic episodes (60%). Reasons for not adding aminoglycosides in the empirical antimicrobial therapy were no necessary combination (46%), other nephrotoxic drugs (24%), aminoglycoside nephrotoxicity (21%), likely not susceptible species (4%), decision of treatment withdrawal (2%), poor penetration (1%), and ototoxic risk (1%).

Among 206 septic episodes, 90 corresponded to the inclusion criteria (half with exclusive IH and half with a combination of IH and CRRT) (Figure), with 16 of the 90 episodes occurring in the same patient with a mean (SD) interval of 16 (6) days (minimum of 8 days) between each. Mean (SD) blood flow was 246 (48) mL/min, mean (SD) dialysate flow was 582 (362) mL/min, mean (SD) fluid removal was 1400 (1300) mL, and mean (SD) blood urea nitrogen was 20 (11)

**Table II. Characteristics of septic episodes for which aminoglycosides were administered in a predialysis vs postdialysis regimen.**

Variable	Predialysis regimen (n = 23)	Postdialysis regimen (n = 16)	<i>P</i>
Patient-related factors			
Male, %	74	67	0.98
SAPS II, mean (SD)	77 (18)	73 (13)	0.52
SOFA score, mean (SD)*	14.6 (4.5)	13.3 (3.1)	0.37
Weight, mean (SD), kg	91 (24)	95 (31)	0.74
Factors related to septic episode			
Infection site (according to AG tissue penetration), %			
Good (abdominal, urinary tract, or blood)	58	42	0.82
Middle (alveolar fluid, skin, or soft tissue)	26	33	
Poor (cerebrospinal fluid or joint) or no identified site	16	24	
Final documentation, %			
Gram negative	55	25	0.25
Gram positive	25	42	
Other (fungi or virus) or no documentation	20	33	
Concomitant nephrotoxic drug (≥1 nephrotoxic drug), %			
Diuretics	21	31	0.76
Iode	17	15	
Vancomycin	28	23	
Amphotericin B	3	0	
Angiotensin receptor blocker	7	0	
No	24	31	

SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

\* SOFA score was calculated at inclusion (ie, the day the aminoglycoside was administered).

mmol/L before the session and 12 (7) mmol/L after the session.

The mean (SD) amikacin and gentamicin doses were 20.6 (6.6) mg/kg and 5.4 (2.5) mg/kg, respectively (n = 90 septic episodes) (Table I), without difference in doses used in septic episodes of patients needing CRRT (n = 145 (Figure) (20.2 [6.6] mg/kg and 6 [1.95] mg/kg, respectively). No significant difference in the mean (SD) number of aminoglycoside administration for 1 septic episode was observed (2.5 [1.6] for amikacin and 2.7 [2.1] for gentamicin; *P* = 0.61). Mean (SD) amikacin and gentamicin  $C_{\max}$  in patients receiving IH were of 55.6 (20.8) mg/L and 20.2 (7.8) mg/L, respectively, without significant difference with those of patients receiving CRRT. No difference was observed for the interval between 2 consecutive doses

of amikacin versus gentamicin (Table II) or between patients receiving IH versus CRRT.

Data including the timing between aminoglycoside administrations and IH sessions could not be analyzed in 46 septic patients in whom aminoglycosides had been administered during CRRT and in whom aminoglycoside administration at the time of IH. In the 44 remaining episodes,  $C_{\max}$  and  $C_{\min}$  are reported in Table I. The perfusion was initiated before IH in 23 (53%), with a mean (SD) interval time of 6.4 (5.2) hours, during IH in 5 (12%), and after IH in 16 (36%), with a mean (SD) delay of 3.4 (4) hours. Table II lists the clinical characteristics of sepsis according to predialysis vs postdialysis administration. The mean (SD) time to the first  $C_{\min}$  target attainment was 33.9 (14.2) hours in the predialysis period versus 50.9 (12.2)

hours in the postdialysis period of administration ( $P = 0.009$ ).

## DISCUSSION

To our knowledge, the present study is the first to report a multicenter, descriptive observation of aminoglycoside administration during IH in critically ill septic patients. Most previous studies have been conducted in quasi-experimental conditions.<sup>12,13,15,21</sup> It is important to provide data exemplifying the real-life management of aminoglycosides. In patients receiving IH, traditional practice included the administration of a postdialysis aminoglycoside corresponding to half the usual dose.<sup>22</sup> More recently, a predialysis aminoglycoside administration schedule produced a 40% decrease of aminoglycoside AUC compared with postdialysis administration.<sup>12</sup> However, the predialysis schedule is still controversial.<sup>16,17</sup> In our study, not all physicians use it. In this study, we quantified its effect as a predialysis schedule translated to a better pharmacokinetic target attainment (mean [SD] time to the first  $C_{\min}$  target of 33.9 [14.2] hour in the predialysis period vs 50.9 [12.2] hours in the postdialysis period). This finding could encourage use of the predialysis administration schedule by physicians who intend to administer at least 2 aminoglycoside doses in patients with septic shock because physicians will rarely reinject aminoglycosides at 50 hours in critically ill patients (because their patient is now stable), whereas they may after 30 hours.

Our study has limitations. The pharmacokinetic properties of aminoglycosides can be modified by patient-related factors (eg, body mass index and chronic kidney disease), disease-related factors (eg, severity of sepsis, volume of fluid expansion, and acute kidney injury), and pathogen-related factors (MIC). Despite presentation by aminoglycoside type before vs after the IH regimen (Table II), no model accounting for individual patient or pathogen factors (no reported  $C_{\max}$ /MIC) was provided. Moreover, age of patients was not collected, although age can play a role in pharmacokinetic properties. The absence of systematic and individual pharmacokinetic assessment of aminoglycoside concentrations for each patient provides data of weaker evidence. This study is not a standardized, prospective study, and we cannot discard a selection bias in favor of the patients receiving the best care. The use of

different dialyzers among the various participating centers could add potential confounding on the study findings.<sup>23</sup>

## CONCLUSIONS

In conclusion, during IH, a significant number of ICU physicians still use a postdialysis schedule of aminoglycoside administration despite a predialysis schedule of administration significantly reducing the interval time to successful aminoglycoside redosing.

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## CONFLICTS OF INTEREST

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

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