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THE NEPHROTOXICITY OF AMINOGLYCOSIDES IN PATIENTS WITH SEVERE SEPSIS OR SEPTIC SHOCK: A PROPENSITY BASED STUDY

Picard W[1*], Bazin F[2], Clouzeau B[1], Bui H-N[1], Soulat M[1], Guilhon E[1], Vargas F[1], Hilbert G[1], Bouchet S[2,3], Gruson D[1], Moore N[2,3], Boyer A[1,2 #].

Service de Réanimation Médicale, CHU Bordeaux, 3 place Amélie Raba-Léon, 33076 Bordeaux cedex [1] ; INSERM, U657 Pharmaco-Epidémiologie et Evaluation de l'Impact des Produits de Santé sur les Populations, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France [2] ; Département de Pharmacotoxicologie CHU de Bordeaux, 3 place Amélie Raba-Léon, 33076 Bordeaux cedex [3]

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Corresponding author. Mailing address: Service de Réanimation Médicale, CHU Bordeaux, 3 place Amélie Raba-Léon, 33076 Bordeaux cedex ; Phone: 05 56 59 55 17, Fax 05 56 59 61 22, Email : alexandre.boyer@chu-bordeaux.fr

* the current affiliation of Walter Picard is: Service de Réanimation Polyvalente, CH Pau, 4 Boulevard Hauterive, 64000 Pau

Abstract

To assess the risk of acute kidney injury (AKI) attributable to aminoglycosides (AG) in patients with severe sepsis or septic shock, we performed a retrospective cohort study in one medical intensive care unit (ICU) in France. Patients admitted for severe sepsis/septic shock between November 2008 and January 2010 were eligible. A propensity score for AG administration was built with day 1 (D1) demographic and clinical characteristics. Patients still on the ICU on D3 were included. Patients with renal failure before D3 or endocarditis were excluded. The time window for assessment of renal risk was D3-D15, defined according to the Risk, Injury, Failure, Loss, and End-Stage Renal Disease (RIFLE) classification. The AKI risk was assessed by means of a propensity-adjusted Cox proportional hazards regression analysis. Of 317 consecutive patients, 198 received AGs. The SAPS II score and nosocomial origin of infection favoured the use of AGs whereas a pre-existing renal insufficiency and the neurological site of infection decreased the propensity for AG treatment. 103 patients with renal failure before D3 were excluded. AG were given once-daily over 2.6±1.1 days. AKI occurred in 16.3% of patients in a median time of 6 [5-10] days. After adjustment to the clinical course and exposure to other nephrotoxic agents between D1 and D3, a propensity-adjusted Cox proportional hazards regression analysis showed no increased risk of AKI in patients receiving AGs (aRR = 0.75 [0.32-1.76]). In conclusion, in critically septic patients presenting without early renal failure, an aminoglycoside therapy for less than 3 days was not associated with an increased risk of AKI.

Introduction

Aminoglycosides (AGs) have a bactericidal activity, which has been proven to be synergic with βlactams. If adding an aminoglycoside (AG) to a standard antibiotic treatment did not translate into a reduction of mortality in NGB sepsis in subgroups of patients with globally moderate degrees of severity (1), a decrease in mortality was recently reported in a meta-analysis comparing a bitherapy versus a βlactam alone in patients with septic shock (2). In addition, AGs widen the spectrum of the antibiotic treatment, which should be advantageous in populations with an increased risk of resistant bacteria, such as intensive care unit (ICU) patients (3, 4). Empiric antibiotic treatments including AGs could be more appropriate in up to 15-20% compared with a βlactam alone (5, 6). In the ICU setting, modifications of the empiric antibiotic treatment or the addition of a new antibiotic occur less frequently after bitherapy including an AG compared with monotherapy (7).

Unfortunately, nephrotoxicity is an important potential limitation of AGs. There is a consensus that AG-related nephrotoxicity has decreased over years due to better consideration of both reduced duration of treatment and once daily administration (8). However, in ICU patients, higher doses have been recommended (9) as an increased volume of distribution (Vd) has been described (10). These aggressive doses could be responsible for higher nephrotoxicity incidence. To date, a decrease in renal function has been observed in 5-14% of patients receiving AGs according to a wide definition (>33% decrease in creatinine clearance (Crcl) ± plasma creatinine increase ≥ 0.3mg/dL) or a more restrictive definition (>50% decrease in Crcl ± plasma creatinine increase ≥ 0.5mg/dL) (11-13). Both definitions may overestimate AG-associated renal toxicity and the addition of criteria for tubular damage to the definitions based on plasma creatinine lowers the incidence of AG-related nephrotoxicity by 2- or 3-fold (13, 14). Conversely, a recent score designed to assess acute kidney injury

(AKI) in severely septic patients (the RIFLE score (15)) found 24% AKI in patients receiving AGs (16).

These controversial data suggest that AG-associated AKI might not be solely attributed to AGs because of the frequent confounding factors associated with AKI (17-19), such as septic shock *per se*, other nephrotoxic drugs (20), direct effect of bacterial toxins and comorbidities such as diabetes or altered baseline renal function. The aim of this study was to assess the AG-attributed AKI (the real AG nephrotoxicity) in patients with septic shock or severe sepsis.

Materials and methods

Design and ethical aspects

This was a retrospective, observational study performed in a single 28-bed medical ICU from November 2008 to January 2010. The study protocol was approved by the Ethical committee of the Société de Réanimation de Langue Française. Written consent was waived because of the observational nature of the study.

Inclusion, exclusion criteria and recruitment period

The first part of the study consisted in including all patients admitted for or who developed septic shock or severe sepsis. Factors associated with the administration of AGs in septic shock or severe sepsis on day 1 (D1) were studied in this first set of patients.

Adult patients still in the ICU on D3 were eligible for inclusion in the second part of the study aiming at the determination of the nephrotoxicity risk associated with AG treatment (primary objective). Patients who had another indication for AG such as endocarditis, even complicated by severe sepsis, were excluded. Patients with renal failure before D3 (either those under chronic renal replacement therapy or with acute tubular necrosis needing renal replacement therapy) were excluded as the distinction between aspecific renal failure and the specific AGs-associated nephrotoxicity would be impossible in these patients. Patients with D1 renal clearance of less than 56.25 ml/mn/1.73m^2 (I category of the RIFLE score (21)) followed by a severe decrease until D3 without the need for renal replacement therapy (D1/D3 renal clearance >1 + D3 renal clearance < 37.5 ml/mn/1.73m^2 before D3) were also excluded, since this decrease cannot either be attributed to AGs. Studied parameters were collected from D1 to the end of study, i.e., D15, day of discharge or day of death when occurring before D15.

Objectives

The primary objective of this study was the assessment of the AKI risk from D3 to D15, in patients having received AGs, in comparison with patients who did not receive AGs.

The secondary objectives were the identification of factors associated with the administration of AGs in severe sepsis or septic shock and the description of AG treatment in a population of ICU patients with severe sepsis or septic shock.

The AKI was defined by the increase of the RIFLE score (21) from

1) (No risk + creatinine clearance > 56.25 ml/mn/1.73m^2 on D3) to (Risk, Injury or Failure from D3 to D15)

2) Risk category (37.5 ml/mn/1,73m^2 <crCl< 56.25 ml/min/1.73m^2) to Injury or Failure.

Creatinine clearance was calculated on a daily basis using daily serum creatinine and the simple modified modification in diet in renal disease (MDRD) which is supposed to provide estimation of the glomerular filtration rate (GFR) (15). For each patient included in the cohort, the charts were reviewed and the following data were recorded: demographic variables, Simplify Acute Physiology Score II (SAPS II) at the end of D1, Sequential Organ Failure Assessment (SOFA) at the end of D1 and D3, type, cause and severity of infection (severe sepsis and septic shock were defined according to the international guidelines (23)), nephrotoxic drugs and intravenous (iv) iodate contrast used at admission and all along the stay, other risk factors for nephrotoxicity (i.e. diabetes mellitus, presence of a single functional kidney, cirrhosis, kidney graft, pre-existing renal failure, rhabdomyolysis (defined by CPK >500 IU/L)).

The duration of therapy, the dose and serum concentrations of AGs were also recorded.

AG treatment

In the ICU, AGs were always combined with βlactams. Gentamicin (G) was recommended for treatment of infections due to Gram-positive or community-acquired Gram-negative

bacteria, whereas amikacin (A) was recommended for treatment of nosocomial-acquired Gram-negative bacteria infections. Tobramycin was not recommended. Doses and adjustments were checked daily by senior physicians with expertise in infectious diseases (AB and DG). The AG loading dose was calculated according to the total body weight (TBW) (20 mg/kg for A and 7 mg/kg for G) (10, 24). This regimen was defined according to an expected mean Vd of 0.3 to 0.4 L/kg and a target peak concentration of 25-30 mg/L for G and 40-50 mg/L for A. If the observed peak was <20 mg/L for G or <35 mg/l for A, the daily dose was increased by 1.25-1.3 fold. Inversely if the peak was >35 mg/L for G or >55 mg/l for A, the daily dose was reduced in the same proportions. If the trough was >2.5 mg/L for G and 5 mg/L for A, the AG injection was delayed until the target trough was obtained. Peak was assessed 30 minutes after the end of AG infusion and trough just before the following one, except for the last administration. A maximum of 5 days of AG therapy was recommended. The area under the curve (AUC) were calculated from the peak and trough of the same interval by using a one-compartment PK model.

Statistical analysis

The categorical variables were compared using Chi-squared test and continuous variables were compared using the Student's *t*. In order to adjust for confounding factors of AKI that could have participated in the decision to administrate AG, a propensity score of AG treatment was built with D1 variables (the day of sepsis and antibiotic initiation). All the variables supposed to interact with the decision were considered. On D3, once patients meeting prespecified criteria had been excluded, the time to AKI was examined by Kaplan-Meier and propensity-adjusted Cox proportional hazards regression analyses. The dependant binary variable was the AKI occurrence and AG treatment was the primary independent variable. Most of the other independent variables having been already considered in the propensity score, only new nephrotoxic treatments (after D1 and until either AKI or the end of

150 the study, i.e. D15 or before if death or discharge), and the evolution of sepsis by delta SOFA
151 (D3-D1) were added to this model. Adjusted relative risks were computed for variables in the
152 final model. A p value of 0.05 was considered significant. All calculations were computed
153 using SAS version 9.3 (SAS corporation, Cary, NC).

154

Results

Day 1 results and propensity score

Between November 2008 and January 2010, 317 adult patients were consecutively included in the study. AGs had been administered to 198 patients. Septic shock was present in 227 (71.6%) whereas 90 (28.4%) had a severe sepsis (table 1). In table 2 are described the variables constituting the propensity score for AG treatment. The most significant factors associated with AG administration were the SAPS II score and the nosocomial origin of infection which both favoured the decision to use AG treatment. In turn, a pre-existing renal insufficiency and the neurological site of infection both decreased the propensity for AG treatment. The distribution of the propensity score for receiving AG according to the true AG administration shows that a number of patients had an intermediate score (data not shown). Once adjusted for the propensity score, no difference between patients receiving or not AGs was observed anymore (data not shown).

Day 3 results

Between D1 and D3, 103 patients among 317 were excluded, among whom 72 for either initial severe AKI (n=58) or renal replacement therapy (n=14) (AGs were administered in two thirds of these patients (n=48)). The remaining population of 214 patients had a mean length of ICU and hospital stay of respectively 16±16 and 38±60 days. Twenty-one died before D15 (10%). Among these 214 patients, 150 received AGs. The mean duration of AG therapy was 2.6±1.1 days. Amikacin was prescribed in 74% and gentamicin in 26%. Results of drug monitoring including trough and peak determinations are shown in table 3. The area under the curve (AUC) of gentamicin was 200±114 mg.h/L and 537±590 mg.h/L for amikacin. Figure 1 represents the distribution of the propensity score, according to whether AGs were given or not, in the 214 patients. AKI occurred in 35 patients (16.3%) with a median delay of 6 [5-10] days. The results of the multivariate analysis of risk factors for acute renal failure are shown

in table 3. The SOFA score improved from D1 to D3 in 154 patients (72%) whereas it decreased in 60 (28%). At least one additional nephrotoxic agent had been administered in 133 patients (62%) in the period from D1 to the index date. Variables associated with the occurrence of AKI risk in the multivariate Cox model are shown in table 4. After adjustment to delta SOFA, exposure to additional nephrotoxic agents (D1-index date), and propensity score for AG treatment, the administration of AGs was not associated with a significant risk of AKI (table 4).

Ninety one patients (28.7%) died before D28 among the entire D1 population and the variables independently associated with the occurrence of death in the multivariate Cox model were age and gender whereas AG treatment was not significantly associated with D28 mortality (table 5).

Discussion

The main finding of our study is that aminoglycosides are not associated with an increase in AKI in patients admitted to ICU for severe sepsis or septic shock without early renal failure after adjustement on the clinical evolution of patients in the first three ICU days (delta SOFA D3-D1 and exposure to nephrotoxic agents) and, most importantly, on the propensity score to receive AGs.

The propensity score was based on the risk factors for AG nephrotoxicity listed in two meta-analyzes (25, 26) to which we added specific characteristics of sepsis. The patient severity (SAPS II score, OR = 1.02 [1.00-1.04]) was a major determinant in the decision to use AGs, reflecting the prescribers' confidence in the bactericidal and synergistic action of AGs (27). Another factor positively influencing AG treatment was the nosocomial origin of infection (OR = 2.10 [1.22-3.63]). This could be expected since hospital infections are commonly caused by multiresistant bacteria (28). Conversely, the neurological origin of sepsis discouraged the initiation of AGs (OR = 0.14 [0.03-0.76]), which is in accordance with their pharmacokinetic characteristics, no more than 10 percents of the total intravenous dose penetrating cerebrospinal fluid (29). Patients with preexisting renal failure (OR = 0.37 [0.14-1.00]) were less prone to be treated by AGs probably due to a benefit-risk approach in this subset of patients.

The overall incidence of AKI in our study was 16% (35/214) which should be considered as low compared to the data of a recent Italian study reporting a 40% incidence of acute renal failure in 279 septic ICU patients (30). This might be explained by our decision to exclude patients with AKI occurring before D3. Adding these excluded patients (n=72) would have led to a comparable overall risk of AKI (37%; 107/286). Many studies have attempted to determine the specific renal risk of AGs and the risk prevalence of AKI is highly variable. The vast majority of published studies suffer from the absence of combination of validated

acute renal failure criteria and sufficient severity of patients to allow the extrapolation of results to critically ill patients. The Acute Dialysis Quality Initiative group developed the RIFLE classification accounting for a broad range of acute impairment of kidney function through consensus of experts (15). It has been validated in ICU patients and can detect AKI with high sensitivity and specificity (15, 21). A recent retrospective study using these criteria has shown a 24% AG nephrotoxicity, but only 12% of patients experiencing AKI had severe sepsis (16). A strength of our study was to use a validated AKI classification in an exclusively ICU population. We also carefully avoided other methodological flaws. Patients with Injury, Failure or Loss of RIFLE score before D3 were excluded in order to increase the specificity of AGs-associated acute renal failure. Indeed, AG-associated nephrotoxicity is known to occur at the end of the AG treatment or later, i.e. from D3 to D15. This time window was chosen based on a previously reported mean delay between AG treatment and nephrotoxicity of 8.8±3.4 days (22).

Moreover, AKI in severe sepsis or septic shock population is a complex issue. While septic shock remains the leading cause of AKI in this population (32), the pressure on renal function is increased by many other factors such as nephrotoxic drugs (20), direct effect of bacterial toxins, vascular nephritis etc.. (33). To better assess the causal link between the administration of AGs and the AKI occurrence, we performed a quasi-randomized study in which all variables supposed to interact with AKI occurrence were considered in a propensity adjusted Cox proportional hazards regression. It would therefore make sense to abandon the assessment of AG nephrotoxicity by the rate of acute renal failure occurring after the administration of AG and to prefer a better methodological assessment of AG-associated AKI (19).

No AG-associated AKI risk was found in this study (adjusted OR 0.75 95%CI [0.32-1.76]), and there might even be a slight trend towards a reduced renal risk in AG patients,

242 considering the study population did not include patients with early acute renal failure. This
243 might be related to both pharmacological and physiological mechanisms. Recent
244 pharmacological concepts of AGs administration such as the once-daily dose schedule for
245 AGs administration which result in a decrease of AG-associated AKI (9) have been respected
246 in the present study as shown by the use of once daily doses of gentamicin and amikacin
247 during a short course achieving a correct rate of target obtention (Table 3). A physiological
248 mechanism has also been suggested by several authors (34-36). Lipcsey et al. compared four
249 groups of pigs (endotoxinemia + tobramycin, endotoxinemia + saline, saline + tobramycin,
250 saline alone) and suggested that sepsis-induced hypoperfusion was predominant over specific
251 AG toxicity on the AKI occurrence (35). More recently, Langenberg et al. compared 3 groups
252 of sheep (*E. coli* infusion, *E. coli* infusion followed by gentamicin IV, control group) and
253 showed a lower rate of NO synthase and hypoxia-inducible factor in the gentamicin group
254 compared to the septic group. This provides evidence that AGs might stop endothelial and
255 cellular signals at the origin of sepsis-related AKI (36).
256 There are some limitations to this study. This was a retrospective cohort study conducted at a
257 single ICU, possibly limiting its extrapolation. Particularly, even if the AG administration was
258 consistent with the standards of care at the time of the study (100% once daily dose, 61% of
259 Cpeak target attainment, short duration) (37), recent recommendations have emphasized the
260 use of higher doses of amikacin (25-30 mg/kg) potentially changing the AG-associated AKI
261 risk (38). The general characteristics of the population are also representative of medical ICU
262 septic patients (SAPS II 59±20, 72% septic shock, mean duration of ICU stay of 14±16 days).
263 In critically ill patients, assessing glomerular filtration rate by mean of serum creatinine can
264 be questioned. Urinary crCl, though more specific, bears the same limitations (39). We used
265 MDRD formula for basal estimation of glomerular filtration rate following recommendation
266 of RIFLE classification. However, recently, the KDIGO (Kidney Disease: Improving Global

Outcomes) initiative proposed a modified RIFLE classification that should be used in the future (40). However, to date, RIFLE remains the most validated classification with more than half a million studied patients. We excluded from the analysis patients who had impaired renal function that worsened between day 1 and day 3 since we expect aminoglycoside nephrotoxicity to be manifest some days after starting. However, we performed a sensitivity analysis in reincorporating patients excluded for initial renal failure (defined by creatinin clearance <37.5) (n=58), and patients needing immediate renal replacement therapy (n=14). Among this population (n=286), 107 (37,4%) patients developed AKI. The AKI adjusted relative risk of aminoglycoside treatment (yes vs. no) given by the Cox model was 0,95 [CI 95% 0,59-1,47], p=0,76. Finally, the finding of no increased risk might be attributed to a lack of power despite the relatively large number of patients included. However, the probability that the trend in the reduction of risk obtained in this study could be reversed to an increase is low, especially with the statistical methods used. With traditional multivariable regression techniques, models become unstable when the sample size is small and the number of covariates included in the model is large relative to the number of outcome events. Adjusting on propensity scores is a mean to prevent from overloading subsequent regression models especially when studying a rare outcome (41). In this case, though the choice of treatment was not randomized, and it might be surmised that these drugs would be used in patients at lower risk of renal failure, the use of a propensity score built with all known risk factors for renal failure should protect against such confounding. Of course the lack of association we found does not mean that AG are no longer nephrotoxic, just that the choice of patients and the way the drugs were given was judicious. Further studies in similar patients in other settings would be useful to confirm these results, and ideally under randomized controlled circumstances, which unfortunately are hardly possible in this context.

291 In conclusion, with modern modalities of administration including high dose once daily and
292 short duration of treatment, AG did not appear to increase the AKI risk in ICU patients treated
293 for severe sepsis or septic shock without early acute renal failure.

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Conflict of interest statement:

The authors have no relevant conflict of interest in the field of aminoglycoside treatment.

Figure legends

Figure 1. Propensity score for aminoglycoside treatment at baseline for the studied patients

309 Table 1. Baseline characteristics of the patients for propensity score elaboration

Variables			Aminoglycosides		
			No	Yes	
		n=317	n=103	n=214	p value
Sex	Male	191 (60.2)	61 (59.2)	130 (60.7)	
Age		59 (17)	59 (16)	59 (18)	0.67
SAPS II		59.2 (20.7)	60.7 (20.2)	56.0 (21.3)	0.06
Nosocomial sepsis	Yes	175 (55.2)	44 (42.7)	131 (61.2)	<10-1
Sepsis origin	Blood or catheter	21 (6.6)	6 (5.8)	15 (7.0)	0.02
	Abdominal, urinary or gynecological tract	34 (10.7)	8 (7.8)	26 (12.1)	
	Lung, skin soft tissue, osteitis or arthritis	232 (73.2)	71 (68.9)	161 (75.2)	
	Neurological	13 (4.1)	8 (7.8)	5 (2.3)	
	No identified origin	17 (5.4)	10 (9.7)	7 (3.3)	
Sepsis severity	Septic shock	227 (71.6)	71 (68.9)	156 (72.9)	0.47
	Severe sepsis	90 (28.4)	32 (31.1)	58 (27.1)	
Number of organ failure	No failure	35 (11.0)	10 (9.7)	25 (11.7)	0.60
	At least one	282 (89.0)	93 (90.3)	189 (88.3)	
Rhabdomyolysis*		40 (12.62)	17 (16.50)	23 (10.75)	0.16
Renal graft or single functional kidney		18 (5.7)	6 (5.8)	12 (5.6)	0.94
Diabetes mellitus		55 (17.3)	14 (13.6)	41 (19.2)	0.21
Cirrhosis		41 (12.93)	11 (10.7)	30 (14.0)	0.40
Preexisting renal failure		30 (9.5)	13 (12.6)	17 (7.9)	0.19
Nephrotoxic treatments					
ACE inhibitors/ARB		85 (27.0)	26 (25.2)	59 (27.8)	0.63
Diuretics		97 (30.8)	29 (28.2)	68 (32.1)	0.48
High osmolar radiocontrast agent		27 (8.6)	10 (9.7)	17 (8.0)	0.62
Hydroxyethil starches		15 (4.8)	5 (4.8)	10 (4.7)	0.96
NSAIds		18 (5.7)	4 (3.9)	14 (6.6)	0.31
Antimicrobial agent°		32 (10.2)	10 (9.7)	22 (10.4)	0.85
Immunosuppressive treatment °°		19 (6.0)	7 (6.8)	12 (5.7)	0.69
Nephrotoxic treatments	No	128 (40.6)	48 (46.6)	80 (37.7)	0.13
	At least one	187 (59.4)	55 (53.4)	132 (62.3)	

310

311 Qualitative variables are represented with n (%), quantitative variables with mean (SD)

312 SAPS Simplified acute physiology score; ACE angiotensin converting enzyme ; ARB

313 angiotensin receptor blockers; NSAIds Non steroidal anti-inflammatory drugs

314 * rhabdomyolysis is defined by CPK>500 IU/L; ° vancomycin, amphotericin B, acyclovir,

315 foscavir; °° calcineurin inhibitors

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317 Table 2. Multivariate analysis of factors associated with aminoglycoside treatment

	Variables	Total	OR [95% CI]
Sex	Male	191 (60.2)	1.00
	Female	126 (39.8)	0.92 [0.52-0.61]
Age		59 (17)	0.99 [0.97-1.01]
SAPS II		59.2 (20.7)	1.02 [1.00-1.04]
Nosocomial sepsis	No	142 (44.8)	1.00
	Yes	175 (55.2)	2.10 [1.22-3.63]
Sepsis origin	Blood or catheter	21 (6.6)	1.00
	Abdominal, urinary or gynecological tract	34 (10.7)	1.25 [0.32- 4.91]
	Lung, skin soft tissue, osteitis or arthritis	232 (73.2)	0.93 [0.31- 2.80]
	Neurological	13 (4.1)	0.14 [0.03- 0.76]
	No identified origin	17 (5.4)	0.23 [0.05- 1.01]
Sepsis severity	Septic shock	227 (71.6)	1.00
	Severe sepsis	90 (28.4)	0.87 [0.43- 1.74]
Number of organ failure	No failure	35 (11.0)	1.00
	At least one	282 (89.0)	0.46 [0.16- 1.30]
Rhabdomyolysis*	No	277 (87.4)	1.00
	Yes	40 (12.6)	0.61 [0.28- 1.30]
Renal graft or single functional kidney	No	299 (94.3)	1.00
	Yes	18 (5.7)	1.53 [0.43- 5.41]
Diabetes mellitus	No	262 (82.6)	1.00
	Yes	55 (17.3)	1.69 [0.78- 3.64]
Cirrhosis	No	276 (87.1)	1.00
	Yes	41 (12.9)	1.53 [0.66- 3.58]
Preexisting renal failure	No	287 (90.5)	1.00
	Yes	30 (9.5)	0.37 [0.14- 1.00]
Nephrotoxic treatments			
ACE inhibitors/ARB	No	230 (73.0)	1.00
	Yes	85 (27.0)	0.81 [0.38- 1.76]
Diuretics	No	218 (69.2)	1.00
	Yes	97 (30.8)	0.70 [0.33- 1.53]
High osmolar radiocontrast agent	No	288 (91.4)	1.00
	Yes	27 (8.6)	0.63 [0.23- 1.73]
Hydroxyethil starches	No	300 (95.2)	1.00
	Yes	15 (4.8)	0.77 [0.21- 2.81]
NSAIds	No	297 (94.3)	1.00
	Yes	18 (5.7)	1.91 [0.47- 7.70]
Antimicrobial agent°	No	283 (89.8)	1.00
	Yes	32 (10.2)	0.97 [0.37- 2.56]
Immunosuppressive	No	296 (94.0)	1.00

treatment °°	Yes	19 (6.0)	0.31 [0.09- 1.03]
Nephrotoxic treatments	No	128 (40.6)	1.00
	At least one	187 (59.4)	1.99 [0.80- 4.95]

Qualitative variables are represented with n (%), quantitative variables with mean (SD)

SAPS Simplified acute physiology score; ACE angiotensin converting enzyme; ARB angiotensin receptor blockers; NSAIds Non steroidal anti-inflammatory drugs

rhabdomyolysis is defined by CPK>500 IU/L; ° vancomycin, amphotericin B, acyclovir, foscavir; °° calcineurin inhibitors

324 Table 3. Drug monitoring parameters of aminoglycoside administration.

325

n = 150	n (%)	Dose (mg/kg)	Duration (days)	Cpeak (mg/L)	Cpeak % of target attainment	Ctrough % of target attainment
Gentamicin	39 (26)	6.0±1.6	2.9±1.1	24.9±11.4 (n=101)	47 (>25mg/L)	85.4 (<2.5mg/L)
Amikacin	111 (74)	18.4±5.5	2.5±1.0	44.3±16.0 (n=259)	66 (>40mg/L)	73.3(< 5mg/L)

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328 Table 4. Multivariate risk for acute kidney injury (cox proportional hazards ratio)

	HR*	IC95%	p
Aminoglycoside (yes vs no)	0.75	[0.32-1.76]	0.51
Decrease in SOFA score between D1 and D3 (yes vs no)	1.02	[0.48-2.15]	0.96
Nephrotoxic treatment after day 1 (yes vs no)	0.75	[0.37-1.51]	0.43

329 *The relative risk has been adjusted on the propensity score

330

331 Table 5. Risk for D28 mortality

	RR* IC95%	p
Aminoglycoside (yes vs no)	0.78 [0.47-1.30]	0.34
Age	1.02 [1.01-1.04]	<0.01
Sexe (female vs male)	0.52 [0.33-0.81]	<0.01
Day 1 SOFA	1.05 [0.98-1.13]	0.16
Severe sepsis vs septic shock	1.05 [0.52-2.09]	0.90

332 *The relative risk has been adjusted on the propensity score and the SAPS II score

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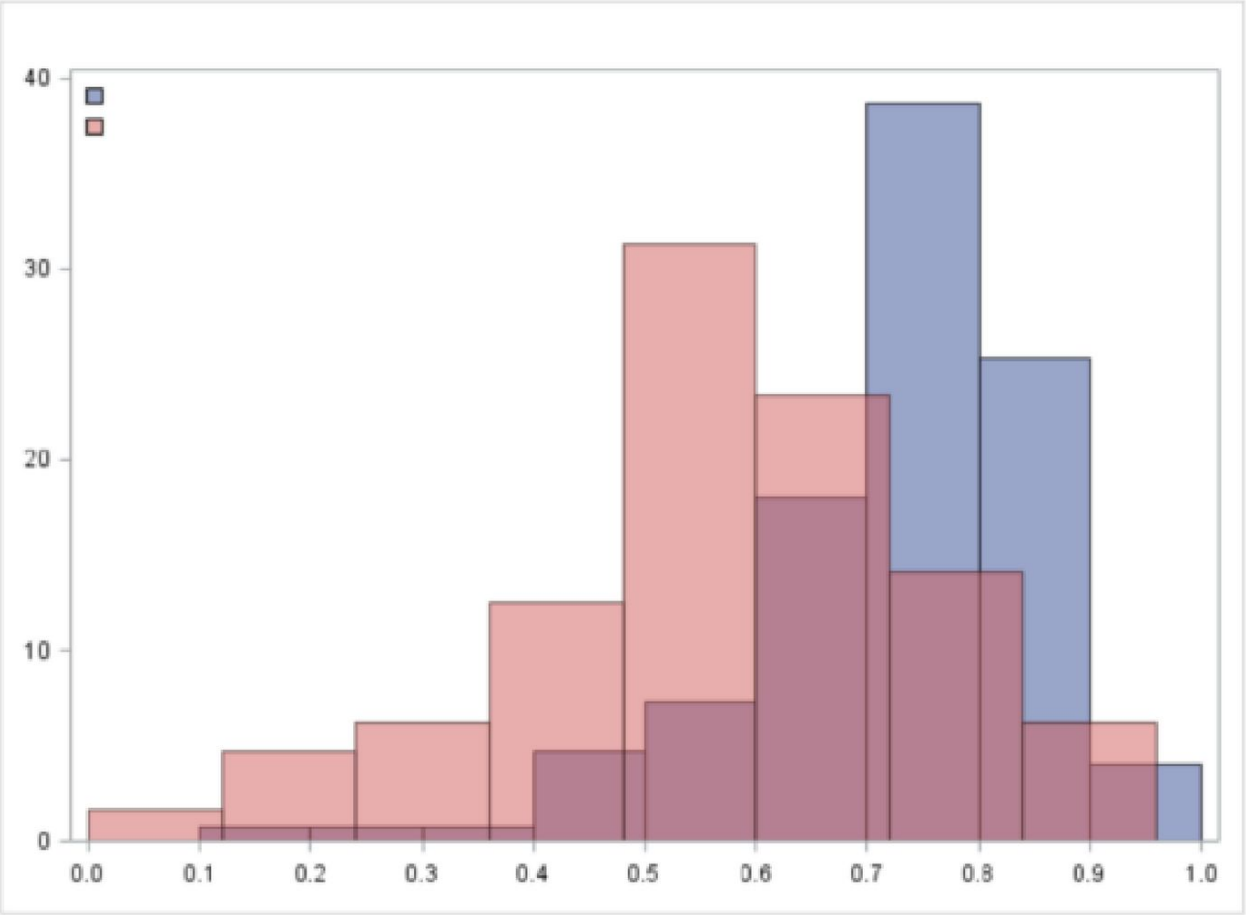

Pink: not treated with AGs; Blue: treated with AGs