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Objectifs PK/PD pour l'amikacine et la gentamicine en réanimation

PK/PD targets of amikacin and gentamicin in ICU patients

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Contribution of authors

A. C. contributed to collecting patient data, analyzing the data, and writing the article. G. D. contributed to designing the study, collecting patient data, and writing the article. L. J. contributed to designing the study and collecting patient data. S. C. and J. C. contributed to the bacteriological analysis. D.B. contributed to writing the article. M. G. contributed to analyzing the data and writing the article. C. B. contributed to designing the study, collecting patient data, analyzing the data, and writing the article.

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Keywords: amikacin, gentamicin, PK/PD, intensive care unit

Résumé

Objectifs. Déterminer la proportion de patients en réanimation présentant un sepsis atteignant les objectifs PK/PD recommandés, après une dose unique de 30 mg/kg d'amikacine ou 8 mg/kg de gentamicine.

Patients et méthodes. Cette étude observationnelle, prospective, monocentrique a inclus 138 patients hospitalisés en réanimation pour sepsis (grave ou choc septique), traités par amikacine (n=89) ou gentamicine (n=49). La concentration (C_{max}) était mesurée 30 minutes après la fin de la perfusion. Les objectifs PK/PD étaient une $C_{max} \geq 60$ mg/L pour l'amikacine et une $C_{max} \geq 30$ mg/L pour la gentamicine en probabiliste, ainsi qu'un ratio $C_{max}/CMI \geq 8$ selon les recommandations françaises.

Résultats. L'index de gravité simplifié (IGS2) médian était 43. La mortalité en réanimation était de 34,8 %. Une documentation bactériologique était présente chez 94 patients (68,1 %). Trois pathogènes présentaient une résistance acquise aux aminosides, et 15 présentaient une résistance naturelle. L'objectif de C_{max} était atteint pour 53 patients (59,6 %) traités par amikacine, et un seul (2,1 %) sous gentamicine. L'objectif de ratio C_{max}/CMI était atteint chez tous les patients présentant une infection documentée à germe sensible (n=72). En régression logistique multivariée, les facteurs associés à l'obtention d'une $C_{max} \geq 60$ mg/L d'amikacine étaient la dose par kilogramme de poids adapté (OR=1,39, $p < 0,001$) et la clairance rénale estimée selon la formule CKD-EPI (OR=0,98, $p = 0,003$).

Conclusions. Malgré de fortes doses d'aminoside, les objectifs de C_{max} ne sont pas fréquemment atteints chez les patients en réanimation. Cependant, un ratio $C_{max}/CMI \geq 8$ était atteint chez tous les patients.

Abstract

Objectives. We aimed to evaluate the probability to achieve PK-PD targets in patients with sepsis hospitalized in the intensive care unit (ICU) after a single dose of 30 mg/kg of amikacin or 8 mg/kg of gentamicin.

Patients and methods. This single-center prospective study included 138 ICU patients with severe sepsis or septic shock with an indication for intravenous amikacin (n=89) or gentamicin (n=49). Maximum concentration (C_{max}) was measured 30 minutes after infusion completion. PK/PD objectives were respectively $C_{max} \geq 60$ mg/L and ≥ 30 mg/L for amikacin and gentamicin for empirical therapy, and a C_{max}/MIC ratio ≥ 8 , as per French guidelines.

Results. The median Simplified Acute Physiology Score II was 43 and ICU case fatality rate was 34.8%. A causative bacterial agent was identified in 94 patients (68.1%). Three pathogens had acquired aminoglycoside resistance and 15 were naturally resistant. The targeted C_{max} for the first dose was achieved in 53 patients (59.6%) receiving amikacin, and one (2.2%) patient receiving gentamicin. C_{max}/MIC ratio ≥ 8 was obtained in all patients infected with susceptible pathogens (n=72). Factors associated with $C_{max} \geq 60$ mg/L of amikacin in multivariate analysis were dose per kg of adapted body weight (OR=1.39, $p < 0.001$) and renal clearance estimated with CKD-EPI formula (OR=0.98, $p = 0.003$).

Conclusions. Despite high dose, amikacin and gentamicin first C_{max} remain dramatically low in ICU patients. However, an adequate C_{max}/MIC ratio was reached in all patients.

Introduction

Despite advances in critical care management, sepsis and septic shock remain major healthcare problems [1]. In-hospital case fatality associated with septic shock in intensive care units (ICU) is estimated around 40% [2,3].

International guidelines for the management of sepsis and septic shock suggest empirical combination therapy targeting the most likely bacterial pathogen(s) for the initial management of septic shock [4]. The addition of an aminoglycoside to the beta-lactam backbone has been associated with a broader and synergic bacterial coverage and with better clinical outcomes [5], but a rapid de-escalation with discontinuation of combination therapy is also recommended within the first few days. As a result, a single infusion of aminoglycoside is often used at the initial phase of the septic shock.

Failure to achieve a plasma peak concentration (C_{max}) above eight times the minimum inhibitory concentration (MIC) of the causative agent ($C_{max}/MIC \geq 8$) has been associated with clinical failure [6]. Using the breakpoints of *Pseudomonas aeruginosa* as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [7], French guidelines recommend targeting an amikacin C_{max} between 60 and 80 mg/L and a gentamicin C_{max} between 30 and 40 mg/L for empirical therapy, which correspond to a C_{max}/MIC ratio between 8 and 10 [8].

Critically ill patients usually display altered pharmacokinetic properties, such as increased volumes of distribution and altered drug clearance, justifying individualized dosing regimens [9] and high doses. For these patients French guidelines suggest using a first dose of aminoglycoside adapted to the patient's weight: 30 mg/kg of amikacin or 8 mg/kg of gentamicin [8]. However, few studies evaluated the impact of high dosage on the first C_{max} .

We performed a study aimed at evaluating the probability to achieve PK-PD targets in critically ill patients with sepsis after a 30 mg/kg dose of amikacin or an 8 mg/kg dose of gentamicin.

Material and methods

Ethics

The Institutional Review Board approved the present observational study. According to European and French laws, patient written informed consent was waived. However, all patients or their surrogates were verbally informed about the process of data collection and could refuse participation.

Inclusion

The present prospective observational cohort study was conducted at the medical ICU of Nantes University Hospital, France. Patients were included if they were aged over 18 years and were treated for sepsis (severe sepsis or septic shock) with a combination therapy including amikacin or gentamicin on the day of enrollment.

As per French guidelines patients received a 30-minute intravenous infusion of either 30 mg/kg of amikacin or 8 mg/kg of gentamicin, diluted in 50 mL of NaCl 0.9%. The peak plasma concentration (C_{max}) sampling had to be performed 30 (+/- 15) minutes after the end of infusion. Samples were taken on K₂EDTA medium and were immediately analyzed after reception at the laboratory. Aminoglycoside concentrations were measured using automated fluorescence polarization immunoassays (Cobas 8,000 kit, Roche, Basel,

Switzerland). The limits of quantifications were 2.5 mg/L and 0.5 mg/L for amikacin and gentamicin, respectively. Only the first C_{max} fulfilling these criteria was selected.

For patients with a body mass index $<30 \text{ kg/m}^2$, total body weight (TBW) was used to calculate aminoglycoside dosage. For patients with a body mass index $\geq 30 \text{ kg/m}^2$, we used the adjusted body weight (ABW) calculated as follow:

$$ABW = \text{ideal body weight (IBW)} + 0.43 (\text{TBW} - \text{IBW})$$

$IBW = \text{height (cm)} - 100 - (\text{height [cm]} - 150) / X$, with $X = 4$ for males and $X = 2.5$ for females

Patients were excluded in case of pregnancy, aminoglycoside allergy, aminoglycoside administration restrictions (*e.g.*, myasthenia), no health insurance, hospital admission for massive burn, and legal protection.

Data collection

Patients' characteristics were recorded at admission and at inclusion. Disease severity was characterized by the Simplified Acute Physiology Score II (SAPS II) at admission [10]. Aminoglycoside was considered to be initiated at patient admission if it was injected within the first 24 hours after ICU admission. The type of infection and microbiological results were collected by two investigators. Disagreements were settled after discussion with a third investigator. Genera, species, and antibiotic susceptibilities were determined with MALDI-TOF mass spectrometry (bioMérieux, Marcy-l'Étoile, France) and broth dilution method using Vitek2 (bioMérieux, Marcy-l'Étoile, France). Isolates were classified as susceptible to the antibiotic according to the EUCAST breakpoints [11]. We categorized intermediate

isolates as resistant isolates. We distinguished pathogens with naturally- and acquired-resistance.

Study endpoints

The main endpoint was the PK/PD target attainment. The absolute targeted C_{max} were ≥ 60 mg/L and ≥ 30 mg/L for amikacin and gentamicin respectively, and C_{max}/MIC ratio ≥ 8 for both antibiotics. The secondary study objective was to assess the factors associated with an amikacin $C_{max} \geq 60$ mg/L. Knowing that the PK/PD target is rarely achieved after an 8 mg/kg dose of gentamicin [12], no statistical analysis was planned for gentamicin-treated patients.

Statistical analysis

A total of 140 patients were included over six months.

Descriptive data is expressed as median [25th – 75th percentiles] for quantitative variables, and as numbers (percentages) for categorical variables. Targeted C_{max} and C_{max}/MIC attainment were considered categorical variables. This last PK/PD target was only calculated for patients infected with susceptible isolates with available MICs for whom a bacterial documentation (*e.g.*, at least one isolated causative bacterium with available MICs) was obtained. For patients with polymicrobial infection, the highest MIC was used. Attainment of C_{max}/MIC ratio ≥ 10 was also recorded, as some studies suggested to use this threshold [6, 13].

Demographics, clinical, and biological factors were tested for association with a $C_{max} \geq 60$ mg/L for patients treated with amikacin. Student's *t*-test or Mann-Whitney test was used for continuous variables, according to the normality of their distribution. Fisher's exact test was used for categorical variables. Factors associated with targeted C_{max} attainment in

univariate analysis ($p < 0.2$) were entered into a multivariate logistic regression analysis. Selection of variables was done using backward and forward selection ($p < 0.05$). Collinearity between independent factors was investigated. When identified, the most clinically relevant factor was chosen. Adjusted odds ratios were obtained with their 95% confidence interval [OR (95% CI)].

Analyses were performed using the R statistical software version 3.4.4 [14]. As some data was missing at random, we handled it with pairwise deletion. A susceptibility analysis using multiple imputations was performed with R package MICE [15].

Results

Study population and infections

One hundred and thirty-eight patients were prospectively included in the study between July 2014 and November 2016 (Table 1). Eighty-nine patients (64.5%) received amikacin and 49 (35.5%) received gentamicin. Patients' characteristics were similar between both groups. When groups were pooled, the median age was 59 [48-68] years. The mean SAPS II was 43 [30-56]. At inclusion, 67 patients (48.6%) were treated with vasopressors and 87 (63.0%) were on mechanical ventilation. The condition of 15 patients (11.0%) required renal replacement therapy. No patient received extracorporeal membrane oxygenation (ECMO). Forty-eight patients (34.8%) died in the ICU.

The main infections were pulmonary infection in 49 patients (35.5%), digestive tract infection in 28 patients (20.3%), genitourinary tract infection in 17 patients (12.3%), catheter-related infection in seven patients (5.1%), bloodstream infection of unknown origin

in seven patients (5.1%), and miscellaneous infections in 19 patients (13.8%). No source of infection was found for 11 patients (8.0%).

Blood cultures were positive for 60 patients (43.5%). Finally, 117 bacteria were isolated from 92 patients of the whole cohort (66.7%). More than one pathogen was isolated from 13 patients (9.4%). The most frequent pathogens were *Escherichia coli* in 32 patients (27.4%), *Staphylococcus aureus* in 17 patients (14.5%), and *Pseudomonas aeruginosa* in 12 patients (10.3%). Fifteen patients (10.9%) were infected with 17 pathogens naturally resistant to aminoglycosides while three pathogens with acquired resistance (two *Enterobacter cloacae* and one *Staphylococcus haemolyticus*) were isolated from three patients (2.2%). All 12 isolated *P. aeruginosa* were susceptible to both aminoglycosides. All susceptible bacteria with available MICs had a MIC ≤ 2 mg/L for amikacin and gentamicin except four with MIC equal to 4 mg/L for amikacin (one *P. aeruginosa*, one *S. aureus*, one *Enterobacter cloacae*, and one *Eikenella corrodens*). None had a MIC equal to 8.

Primary outcome

The median dose of amikacin was 28.8 mg/kg [range 24.3-30.3] of ABW (Table 3). The median C_{max} was 63.3 mg/L [range 48.8-82.2]. Of 89 patients receiving amikacin, 53 patients (59.6%) had a $C_{max} \geq 60$ mg/L and were considered to have reached the targeted C_{max} . Twenty-four patients (27.0%) displayed $C_{max} > 80$ mg/L.

The median dose of gentamicin was 7.6 mg/kg of ABW [range 6.4-8.7]. The median C_{max} was 17.6 mg/L [range 14.4-22.9]. Out of 49 patients receiving gentamicin, only one patient (2%) had a $C_{max} \geq 30$ mg/L and was then considered to have reached the targeted C_{max} . No patient had a $C_{max} > 40$ mg/L.

In the whole cohort, MICs were available for 93 bacteria recovered from 81 patients (54 patients of the amikacin group and 27 of the gentamicin group). The median C_{max}/MIC ratio was 29.3 [range 21.7-39.7] when only considering patients infected with susceptible pathogens (n=72). A C_{max}/MIC ratio ≥ 8 was obtained for all patients. A C_{max}/MIC ratio ≥ 10 was obtained for 70 patients (97.2%). One patient with a C_{max}/MIC between 8 and 10 was treated with amikacin for a pulmonary infection due to *P. aeruginosa* with a MIC of 4 mg/L. A second patient reached a very low C_{max} of 9.1 mg/L after a 6.1 mg/kg of ABW dose of gentamicin.

Secondary outcome

Factors associated with targeted C_{max} attainment in univariate analysis in the amikacin group were a higher age, a lower renal clearance calculated with the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation, a higher dose per kg of ABW, and a lower time period between the start of the infusion and C_{max} measurement. Results are shown in Table 4. We could not assess the glomerular filtration rate based on urinary creatinine excretion due to missing data. Estimation of creatinine clearance with CKD-EPI equation was better correlated with C_{max} attainment than creatinine clearance estimated with the Modification of Diet in Renal Disease (MDRD) and Cockcroft creatinine equations. In multivariate analysis, only the dose per kg of ABW (OR=1.38, 95% CI [1.21-1.63], $p<0.001$) and renal clearance calculated with CKD-EPI equation (OR=0.98, 95% CI [0.96-0.99], $p=0.003$) remained in the model (Table 5). Susceptibility analysis did not show major differences.

Discussion

The first objective of this study was to determine PK/PD target attainment after one administration of 30 mg/kg of amikacin or 8 mg/kg of gentamicin. We observed that only 59.6% and 2.1% of ICU patients achieved C_{max} targeted by French guidelines (*i.e.*, 60 mg/L for amikacin and 30 mg/kg for gentamicin) after a first dose of 30 mg/kg of amikacin or 8 mg/kg of gentamicin, respectively. Other studies reported that between 76% and 81.8% [12, 16, 17] of patients with severe sepsis treated with 30 mg/kg of amikacin reached the same target. Our relatively lower proportion of patients achieving C_{max} target is not explained by our patients' initial presentation severity, since SAPS 2 score are comparable, nor by the measurement of C_{max} as it was a prospective study with standardized aminoglycoside injection and aminoglycoside concentration measurements.

To our knowledge the present study includes the largest cohort to have been selected to analyze C_{max}/MIC ratios. Two thirds of our patients had bacteriological documentation. We observed that despite a dramatically low C_{max} target attainment frequency, a C_{max}/MIC ratio ≥ 8 was obtained in all cases when considering susceptible pathogens. Median C_{max}/MIC ratio was 29.3 [range 21.7-39.7]. Interestingly, our bacterial local ecology seems favorable to aminoglycoside therapy, with only three bacteria with acquired resistance to aminoglycoside among the 117 bacteria isolated, four susceptible bacteria with MICs of 4 mg/L and no susceptible bacterium with MIC of 8 mg/L. This cannot be explained by a large proportion of community-acquired infections, as <40% of patients were treated by aminoglycoside on admission to the ICU. Sites of infection are similar to other ICU studies [18], as well as causative bacterial species. Similar results were reported in a French study by Roger *et al.* All isolated strains had MICs ≤ 4 mg/L. The authors reported that 15/16 patients who received amikacin and 5/5 patients who received gentamicin reached a $C_{max}/MIC > 10$. Other studies, however, reported a median C_{max}/MIC ratio of 12.5 in patients mainly infected with *P.*

aeruginosa and *Acinetobacter baumannii* after a 30 mg/kg dose of amikacin [16]. A mean C_{max}/MIC ratio of 21.3 for Enterobacteriaceae and 10.3 for *P. aeruginosa* after a 7 mg/kg dose of gentamicin was also reported [19].

C_{max} targets have not been correlated with clinical outcomes in large studies. Moore *et al.* correlated in univariate analysis a maximal and a mean peak plasma level to a successful outcome of Gram-negative pneumonia [20]. This data comes from 37 patients treated with three injections per day of aminoglycoside, and the threshold for amikacin was 28 mg/L. Allou *et al.* included 110 patients receiving 30 mg/kg of amikacin for severe sepsis or septic shock in a prospective observational study [17]. The authors observed in multivariate analysis that the mortality rate was significantly lower in the group of patients with a C_{max} between 60 and 80 mg/L than in the group of patients with a $C_{max} >80$ mg/L (OR 3.95, $p=0.004$), but they reported no difference with the group of patients with a $C_{max} <60$ mg/L (OR 1.92, $p=0.4$).

However, the C_{max}/MIC ratio has been positively associated with clinical outcome. Moore *et al.* observed by multivariate logistic regression that the maximal C_{max}/MIC ratio obtained after several days and a three times a day aminoglycoside course was correlated with clinical response in patients infected with Gram-negative bacteria [6]. A C_{max}/MIC ratio ≥ 8 would lead to $>85\%$ response rate, and a C_{max}/MIC ratio ≥ 10 to $>90\%$ response rate. Kashuba *et al.* estimated by logistic regression a 90% probability of temperature resolution and leukocyte count resolution by day 7 if a C_{max}/MIC ratio ≥ 10 was achieved within the first 48 hours of aminoglycoside therapy in patients with nosocomial pneumonia [13]. *P. aeruginosa* was the predominant pathogen (59%). Zelenitsky *et al.* predicted $\geq 90\%$ probability of cure when C_{max}/MIC was at least 8 in patients with *P. aeruginosa* bacteremia [21]. Additionally, *in vitro*

studies suggest achieving high aminoglycoside concentrations to benefit from the post-antibiotic effect. Blaser *et al.* demonstrated with an *in vitro* pharmacokinetic model >99% reduction of the bacterial counts within 4 hours at peak concentrations >3×MIC. A bacterial regrowth would occur within 24 hours unless the peak concentration/MIC ratio exceeded 8 [22].

The risk of using high aminoglycoside dosage is yet to be defined. Toxicity of aminoglycoside has been related to the trough concentration (C_{trough}) in multiple-day courses. Nevertheless, there is a lack of data on aminoglycoside-related toxicity of a unique dose, as well as on short courses with one daily dose.

The results of this study suggest that, according to our favorable local susceptibility pattern, we could have lowered our C_{max} targets. However, aminoglycosides are often used for the empirical antimicrobial treatment of septic shock and the risk of not being effective on difficult-to-treat susceptible pathogens with high MICs cannot be taken. Dubois *et al.* assessed antibiotic resistance rates among 226 isolates of *P. aeruginosa* isolated in community settings in 2008 [23]. Sixty-one per cent of the strains displayed a MIC of 8 mg/L. Further and updated studies on bacterial susceptibility pattern are needed to determine the actual proportion of pathogens presenting with a MIC of 8 mg/L.

The second objective of this study was to determine the factors associated with targeted C_{max} attainment. Multivariate analysis of factors associated with amikacin $C_{\text{max}} \geq 60$ mg/L retained higher dose per kg of ABW and lower renal clearance calculated with CKD-EPI formula. Renal clearance is not usually associated with C_{max} . We hypothesize that C_{max} , as defined in this study (*i.e.*, concentration measured 30 minutes after the end of a 30-minute injection), does not really correlate with the maximum concentration, which would occur at

the end of aminoglycoside injection. Drug clearance would have already begun at the time of measurement. De Montmollin *et al.* did not find any relation between renal clearance and C_{\max} target attainment [24] in a mixed model multivariate analysis of 181 episodes of amikacin administrations. The authors concluded that in their final model positive 24h fluid balance and BMI $<25 \text{ kg/m}^2$ were predictive factors of $C_{\max} <60 \text{ mg/L}$. Taccone *et al.* did not observe this correlation between fluid balance and C_{\max} in a linear regression model [25]. Twenty-four-hour fluid balance was not recorded in the present study. Change in total body weight and in protein serum level between admission and inclusion were analyzed as a substitute and were not significantly associated with targeted C_{\max} attainment.

ABW has been used for dose calculation to avoid overestimation of amikacin distribution volume in obese patients, as supported by many studies [26–29]. However, our results suggest that the first dose calculation should not only depend on ABW, as the dose per kg of ABW remained significantly associated with C_{\max} target attainment. Pharmacokinetics studies are necessary to create tools helping clinicians to better choose the first dose of aminoglycoside, such as dosing nomogram based on population pharmacokinetic model [30].

Some limitations to this study should be declared. First, it is a single-center study performed in a medical ICU of a tertiary university hospital, and our results may not be generalizable to other ICUs, in particular regarding our local bacterial susceptibility pattern. Second, aminoglycoside-related toxicity and clinical outcome (other than in-ICU mortality) were not recorded. The present study was not designed to evaluate the impact of an aminoglycoside dose on patient outcome. Third, trough aminoglycoside concentrations and subsequent doses were not recorded, as aminoglycosides are often used as a single-dose treatment in

our unit. Fourth, the Vitek system does not always give the exact MICs. Finally, estimation of creatinine clearance using CKD-EPI formula is unsatisfactory in ICU patients. Moreover, we included patients treated with renal replacement therapy in our analysis.

Conclusions

Despite high loading doses, only 59.6% of ICU patients treated with 30 mg/kg of ABW of amikacin achieved the targeted C_{max} , and 2.1% of patients treated with 8 mg/kg of ABW of gentamicin. However, all patients reached a C_{max}/MIC ratio ≥ 8 , questioning recommended C_{max} targets. A high dose per kg of ABW and a low renal clearance were associated with amikacin $C_{max} \geq 60$ mg/L in multivariate logistic regression.

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Table 1. Characteristics of patients**Tableau 1.** Caractéristiques des patients

At ICU admission	TOTAL	amikacin therapy	gentamicin therapy
Patients, n (%)	138 (100.0)	89 (64.5)	49 (35.5)
Age (years), median [IQ1-IQ3]	59 [48-68]	58 [47-68]	60 [53-67]
Male sex, n (%)	81 (58.7)	55 (61.8)	26 (53.1)
Simplified Acute Physiology Score 2, median [IQ1-IQ3]	43 [30-56]	44 [31-56]	43 [27-56]
Height (cm), median [IQ1-IQ3]	170 [160-176]	172 [165-179]	167 [160-173]
Weight (kg), median [IQ1-IQ3]	73.0 [60.0-86.0]	74.5 [63.4-85.8]	69.3 [58.3-85.9]
Adjusted body weight (kg), median [IQ1-IQ3]	70.8 [60.0-81.1]	73.3 [62.6-82.1]	65.7 [57.0-80.1]
Body mass index (kg/m ²), median [IQ1-IQ3]	25.1 [22.0-29.5]	25.0 [22.2-28.6]	25.1 [22.0-31.1]
Patients with BMI \geq 30 kg/m ² , n (%)	29 (21.0)	17 (19.1)	12 (24.5)
Body surface - Dubois formula (m ²), median [IQ1-IQ3]	1.82 [1.65-2.01]	1.84 [1.71-2.01]	1.73 [1.59-2.00]

Protein serum level (g/L), median [IQ1-IQ3]	59.0 [51.0-67.8]	59.0 [52.0-67.0]	61.0 [49.0-68.0]
At initiation of aminoglycoside therapy			
Aminoglycoside initiation at admission, n (%)	56 (40.6)	34 (38.2)	22 (44.9)
Creatinine plasma concentration (μmol/L), median [IQ1-IQ3]	100.0 [69.0-185.0]	103.0 [69.0-191.0]	91.5 [73.8-160.0]
Creatinine clearance estimation - Cockroft, median [IQ1-IQ3]	70.6 [36.6-111.7]	77.2 [37.5-115.0]	68.3 [30.1-102.1]
Creatinine clearance estimation - MDRD, median [IQ1-IQ3]	61.9 [31.8-103.2]	61.1 [31.2-105.0]	62.8 [33.8-94.6]
Creatinine clearance estimation - CKD-EPI, median [IQ1-IQ3]	63.0 [31.4-98.3]	59.8 [31.4-99.1]	63.4 [32.4-92.8]
Weight difference since admission (%), median [IQ1-IQ3]	100.0 [100.0-105.4]	100.0 [100.0-105.1]	100.0 [100.0-105.6]
Protein serum level difference since admission (%), median [IQ1-IQ3]	100.0 [92.0-101.3]	100.0 [92.5-102.0]	100.0 [89.6-100.0]
Vasopressors n (%)	67 (48.6)	46 (51.7)	21 (42.9)
Mechanical ventilation, n (%)	87 (63.0)	60 (67.4)	27 (55.1)
Renal replacement therapy, n (%)	15 (11.0)	9 (10.2)	6 (12.3)
Death in ICU, n (%)	48 (34.8)	33 (37.1)	15 (30.6)

Table 2. Sites of infection and isolated bacteria

Tableau 2. Sites infectieux et documentation bactériologique

Patients with ≥ 1 isolated pathogen(s), n (%)	92 (66.7)
Patients with >1 isolated pathogens, n (%)	13 (9.4)
Patients with ≥ 1 naturally resistant pathogen(s), n (%)	15 (10.9)
Patients with ≥ 1 pathogen(s) with acquired resistance, n (%)	3 (2.2)
MIC of amikacin, median [IQ1-IQ2]	2 [2-2]
MIC of gentamicin, median [IQ1-IQ2]	1 [0.5-1]
Sites of infection (138 patients), n (%)	
Pulmonary	49 (35.5)
Digestive	28 (20.3)
Genitourinary	17 (12.3)

Catheter-related infection	7 (5.1)
Bloodstream infection of unknown origin	7 (5.1)
Other	19 (13.8)
Unknown	11 (8.0)

Isolated bacteria (117 among 138 patients), n (%)

Gram-negative bacilli	79 (67.5)
<i>Escherichia coli</i>	32 (27.4)
<i>Pseudomonas aeruginosa</i>	12 (10.3)
<i>Enterobacter</i> sp.	11 (7.9)
<i>Klebsiella pneumoniae</i>	6 (5.1)
<i>Serratia marcescens</i>	6 (5.1)
<i>Proteus</i> sp.	5 (4.3)
Other	7 (6.0)

Gram-positive cocci	32 (27.4)
<i>Staphylococcus aureus</i>	17 (14.5)
<i>Streptococcus pneumoniae</i>	2 (1.7)
<i>Enterococcus</i> sp.	4 (3.4)
Other	9 (7.7)
Anaerobic bacteria	4 (3.4)
Other*	2 (1.7)

* One *Listeria monocytogenes* and one *Eikenella corrodens*

Table 3. Aminoglycoside therapy**Table 3.** Traitement par aminoglycoside

	amikacin therapy (n=89)	gentamicin therapy (n=49)
Dose (mg/kg ABW), median [IQ1-IQ3]	28.8 [24.3-30.3]	7.6 [6.4-8.7]
Infusion volume (cL), median [IQ1-IQ3]	50 [50-50]	50 [50-50]
Time of infusion (minutes), median [IQ1-IQ3]	30 [30-30]	30 [30-30]
Time between end of infusion and blood sampling (minutes), median [IQ1-IQ2]	30 [30-33]	30 [30-34]
C _{max} (mg/L), median [IQ1-IQ3]	63.3 [48.8-82.2]	17.6 [14.4-22.9]
C _{max} ≥peak target, n (%)	53 (59.6)	1 (2.1)
C _{max} ≥80 mg/L (amikacin) or 40 mg/L (gentamicin), n (%)	24 (27.0)	0
Patients infected with susceptible pathogens, n (%)	49 (55.1)	25 (51.0)
C _{max} /MIC ratio, median [IQ1-IQ3]*	32 [22.9-41.3]	23.2 [16.5-30.8]

$C_{\max} \geq 8 \times \text{CMI}, n (\%)^*$	48 (100.0)	24 (100.0)
$C_{\max} \geq 10 \times \text{CMI}, n (\%)^*$	47 (97.9)	23 (95.8)

*Calculated for patients infected with pathogens susceptible to aminoglycoside and with available MICs (n=72)

Table 4. Association with targeted C_{max} attainment in univariate analysis

Tableau 4. Analyse univariée sur l'obtention de la C_{max} cible

	$C_{max} < 60$ mg/L (n=37)	$C_{max} \geq 60$ mg/L (n=54)	<i>p</i> -value
Age, median [IQ1-IQ2]	54 [43-65]	59 [49 - 68]	0.09
Time between beginning of infusion and blood sampling (minutes), median [IQ1-IQ2]	60.5 [60.0-67.75]	60.0 [60.0-63.0]	0.13
Dose per kg of ABW, median [IQ1-IQ2]	24.1 [19.2-28.8]	30.0 [27.9-30.8]	<0.01
Creatinine clearance estimation - CKD-EPI, median [IQ1-IQ2]	88.0 [46.8-106.5]	48.0 [26.0-94.3]	0.02