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# Predictors of insufficient peak amikacin concentration in critically ill patients on extracorporeal membrane oxygenation

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## Abstract

**Background:** Amikacin infusion requires targeting a peak serum concentration ( $C_{\max}$ ) 8–10 times the minimal inhibitory concentration, corresponding to a  $C_{\max}$  of 60–80 mg/L for the least susceptible bacteria to theoretically prevent therapeutic failure. Because drug pharmacokinetics on extracorporeal membrane oxygenation (ECMO) are challenging, we undertook this study to assess the frequency of insufficient amikacin  $C_{\max}$  in critically ill patients on ECMO and to identify relative risk factors.

**Methods:** This was a prospective, observational, monocentric study in a university hospital. Patients on ECMO who received an amikacin loading dose for suspected Gram-negative infections were included. The amikacin loading dose of 25 mg/kg total body weight was administered intravenously and  $C_{\max}$  was measured 30 min after the end of the infusion. Independent predictors of  $C_{\max} < 60$  mg/L after the first amikacin infusion were identified with mixed-model multivariable analyses. Various dosing simulations were performed to assess the probability of reaching 60 mg/L  $< C_{\max} < 80$  mg/L.

**Results:** A total of 106 patients on venoarterial ECMO (VA-ECMO) (68%) or venovenous-ECMO (32%) were included. At inclusion, their median (1st; 3rd quartile) Sequential Organ-Failure Assessment score was 15 (12; 18) and 54 patients (51%) were on renal replacement therapy. Overall ICU mortality was 54%.  $C_{\max}$  was  $< 60$  mg/L in 41 patients (39%). Independent risk factors for amikacin under-dosing were body mass index (BMI)  $< 22$  kg/m<sup>2</sup> and a positive 24-h fluid balance. Using dosing simulation, increasing the amikacin dosing regimen to 30 mg/kg and 35 mg/kg of body weight when the 24-h fluid balance is positive and the BMI is  $\geq 22$  kg/m<sup>2</sup> or  $< 22$  kg/m<sup>2</sup> (Table 3), respectively, would have potentially led to the therapeutic target being reached in 42% of patients while reducing under-dosing to 23% of patients.

**Conclusions:** ECMO-treated patients were under-dosed for amikacin in one third of cases. Increasing the dose to 35 mg/kg of body weight in low-BMI patients and those with positive 24-h fluid balance on ECMO to reach adequate targeted concentrations should be investigated.

**Keywords:** Amikacin, Pharmacokinetics, Acute respiratory distress syndrome, Cardiac failure, Shock, Volume of distribution

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## Background

Over the last decade, a growing number of patients have benefited from extracorporeal membrane oxygenation (ECMO) as rescue therapy for patients suffering from severe acute respiratory distress syndrome (ARDS) or refractory cardiogenic shock [1]. More than half of them will require antibiotic therapy during their ECMO run to treat a primary infection or secondary acquired infection [2]. Because little is known about the impact of ECMO on antibiotic pharmacokinetics (PK), antibiotic administration on ECMO remains a challenge. Although suboptimal antibiotic dosing in this complex group of patients may have fatal consequences, available data are actually limited to animal [3], simulated ex-vivo [4], or small retrospective human studies [5]. Sequestration in the circuit, increased volumes of distribution (Vd), and decreased drug clearance have been implicated to explain antibiotic–PK modifications in that context [6]. Moreover, the underlying disease in these extremely severely ill patients may also be key. Empirical combination antibiotic therapy, aimed at covering Gram-negative bacilli, usually combines a  $\beta$ -lactam and an aminoglycoside [7]. Considering its good bactericidal activity against *Pseudomonas aeruginosa* and its low resistance rate observed with other Gram-negative bacilli, amikacin is frequently used in that context [8]. Its antibacterial effect is determined by the ratio of peak serum concentration ( $C_{max}$ ) to the targeted pathogen's minimal inhibitory concentration (MIC), with optimal antibacterial activity obtained with a  $C_{max}/MIC$  ratio of 8–10. Consequently, the amikacin  $C_{max}$  range should be 64–80 mg/L [9], while the most recent French guidelines recommended  $C_{max} > 60$  mg/L [10]. Despite administering an amikacin dose of 25 mg/kg total body weight (TBW), only 67–72% of intensive care unit (ICU) patients have been found to achieve that objective [11, 12]. In this setting, further PK changes in ECMO-treated patients would be anticipated. Therefore, this open-label, monocentric, prospective study was designed to determine the frequency and identify factors predictive of insufficient amikacin  $C_{max}$  in critically ill patients, and to analyze the probability of attaining the established PK target (i.e. greater than 60 mg/L but below 80 mg/L).

## Methods

### Setting

This prospective observational study was conducted in a 26-bed medical–surgical ICU at a university hospital. Its protocol was in accordance with the ethical standards of our hospital's Institutional Review Board (Committee for the Protection of Human Subjects). In accordance with French law, informed consent was not obtained for demographic, physiological and hospital-outcome data analyses because this observational study did not modify

existing diagnostic or therapeutic strategies. However, patients and/or relatives were informed about the anonymous data collection and that they could decline inclusion. This database was registered at the Commission Nationale l'Informatique et des Libertés (CNIL, registration number 1950673).

### Study design and patients

We prospectively included all consecutive patients, from January 2015 through February 2016, who received an intravenous amikacin loading dose for suspected Gram-negative infection in a context of venoarterial (VA) or venovenous (VV) ECMO in our ICU. Only the first dose of amikacin was studied. Four types of ECMO systems with poly-4-methyl-1-pentene membrane oxygenators (PLS system, Cardiohelp system, both Maquet, Rastatt, Germany; Hilite 7000 LT system, Medos, Stolberg, Germany; ECC.05 system, Sorin, Mirandola, Italy) were used during the study period. Exclusion criteria were (1) incorrect amikacin regimen ( $< 23$  or  $> 27$  mg/kg TBW); (2) incorrect time of amikacin infusion ( $\pm 5$  min); or (3) incorrect time ( $\pm 5$  min) or absence of  $C_{max}$  determination. Patients with incorrect time of trough serum concentration ( $C_{min}$ ) determination ( $\pm 1$  h) were not excluded if  $C_{max}$  had been obtained correctly.

### Amikacin administration and serum-concentration dosage

Amikacin was administered according to our ICU's written standardized protocol: 25 mg/kg TBW (weighing bed weight of the day), diluted in 50 mL of 0.9% NaCl and continuously infused over 30 min. When the patient's weight was  $> 120$  kg, a maximum of 120 kg was considered to calculate the loading amikacin dose (five patients in our study).  $C_{max}$  was assessed 30 min after that infusion ended and  $C_{min}$  24 h after the latter. Our Microbiology Laboratory used a fluorescence-polarization immunoassay to determine amikacin concentrations, as a routine procedure available 24 h/day, 7 days/week [13].

### Data collection

Demographic data, Simplified Acute Physiology Score (SAPS) II [14], and reason for ECMO were collected for all patients. ECMO-membrane duration was defined as the delay between membrane first use and the time of amikacin infusion. Organ dysfunction at inclusion (i.e. the day of amikacin administration) was assessed with the Sequential Organ-Failure Assessment (SOFA) score. In addition, laboratory tests, including coagulation parameters, complete blood count, electrolytes, liver enzymes, urea, creatinine, and bilirubin, were run. At inclusion, the inotrope score was calculated [15], defined as:

Dobutamine dose ( $\gamma/kg/min$ ) + [Norepinephrine dose ( $\gamma/kg/min$ ) + Epinephrine dose ( $\gamma/kg/min$ )]  $\times 100$ .

The 24-h fluid balance was defined as the difference between fluid intake and fluid output over the 24 h

before amikacin infusion. Proteinemia and hematocrit changes during the 24 h preceding inclusion were calculated as follows:

$$(X_{0h} - X_{24h}) / (X_{0h} + X_{24h}) / 2.$$

In addition, renal function was characterized according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification [16]. Acute renal failure in ICU survivors was defined as KDIGO  $\geq 2$ . Lastly, infection sites and identified pathogens were noted.

### Statistical analyses

Categorical variables are expressed as number (percentage) and compared using the chi-square test. Continuous variables are expressed as medians (1st; 3rd quartile) and compared using Student's *t* test or Wilcoxon's signed-rank test. Pre-amikacin infusion factors associated with a  $C_{max} < 60$  mg/L or a  $C_{max} > 80$  mg/L were selected using univariable mixed models. Demographics and clinical and biological factors with a *p* value  $\leq 0.10$  in our univariable analyses were entered into the multivariable mixed model. The list of data entered in both models is provided in Additional file 1: Table S1. Few relevant variables with a plausible clinical link despite a value of *p*  $> 0.10$  in the univariate analysis were forced into the models (Additional file 1: Table S1). Continuous variables were transformed into categorical variables (the optimal thresholds were defined by analyzing mortality in each corresponding variable quartile). Thereafter, multiple backward-stepwise logistic-regression analyses eliminated variables with an exit threshold set at *p*  $> 0.05$ . All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. In the case of collinearity between factors, the most clinically relevant factor was chosen to construct the multivariable model. Results are reported as odds ratios (ORs) and their 95% confidence intervals (CIs).

Given the observed  $C_{max}$  and the administered dose/kilogram, we assumed amikacin PK linearity [17–20] to simulate individual  $C_{max}$  for the following dosing regimen: 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg TBW. In order to provide dosing regimen recommendations, for each dosing regimen, we estimated the probability of  $C_{max}$  in the therapeutic range (60–80 mg/L) for the different categories of the risk factors found predictive of under-dosing in the multivariable analysis.

Analyses were computed using StatView v5.0 (SAS Institute, Cary, NC, USA), SPSS v22.0 software (SPSS, Chicago, IL, USA) and R v3.3.0 (<http://www.R-project.org>).

## Results

### Study population

During the study period, among 302 ECMO-treated patients in our ICU, 119 (39%) received an amikacin

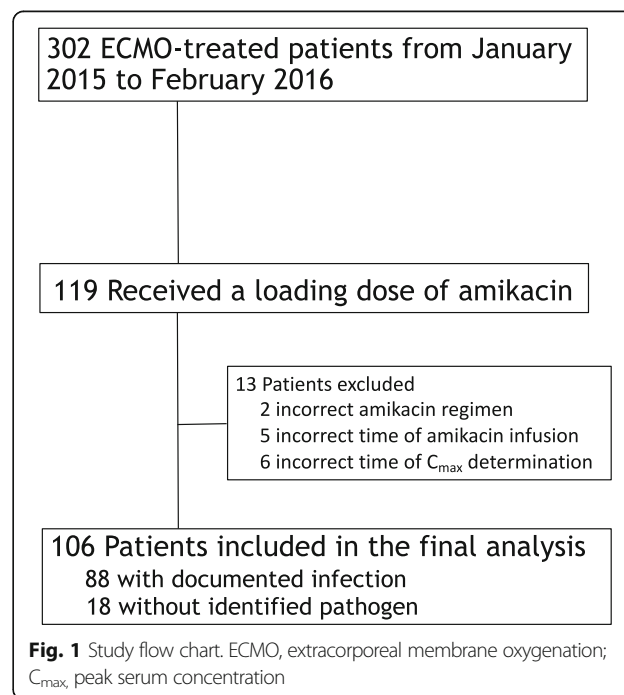
loading dose for severe sepsis or septic shock; 13 were excluded from our analysis for the main reasons listed in Fig. 1. Consequently, PK of a first amikacin loading dose on ECMO were studied in 106 patients. Patient characteristics at ICU admission and study inclusion are shown in Table 1. Median (IQR) age was 55 (45; 62) years, while median SAPS II was 68 (47; 81). VA-ECMO supported 68% of the patients. On the day of amikacin infusion, the SOFA score was 15 (12; 18) with 54 (51%) patients on renal replacement therapy. The main infection sites were lung and cannula for, respectively, 77% and 14% patients, with associated bacteremia in 15 (17%); the most frequently identified pathogens were *P. aeruginosa*, *Enterobacter* spp. and *Escherichia coli* (Additional file 1: Table S2).

### Pharmacokinetic parameters

Amikacin PK parameters are reported in Table 2. The median ECMO cannulation-to- $C_{max}$  interval was 9 (5; 15) days. After receiving a loading dose of 25 (24; 25.5) mg/kg TBW, median  $C_{max}$  was 65.8 (51.8; 82.4) mg/L.  $C_{max}$  was  $< 60$  mg/L in 41 patients (39%) and  $> 80$  mg/L in 27 (25%) (Additional file 1: Figure S1). Median  $C_{min}$  for 85 patients was 7.25 (3.6; 13.6) mg/L, with only 24 patients (28%) having a value  $< 2.5$  mg/L.

### Factors predictive of $C_{max} < 60$ mg/L

Univariable analyses selected lower body mass index (BMI), higher liver-enzyme concentrations, lower proteinemia, lower hematocrit and positive 24-h fluid balance as factors predictive of  $C_{max} < 60$  mg/L (Table 1).



**Table 1** Total population characteristics and univariable analyses of factors predictive of amikacin  $C_{\max} < 60$  mg/L

Characteristic	Total population (n = 106)	$C_{\max} < 60$ mg/L (n = 41)	$C_{\max} \geq 60$ mg/L (n = 65)	p
At ICU admission				
Age, years	55 (44–62) <sup>a</sup>	54 (39–64)	57 (48–60)	0.61
Male	77 (73)	28 (68)	49 (75)	0.42
SAPS II	68 (47; 81)	70 (46; 81)	68 (47; 81)	0.66
BMI, kg/m <sup>2</sup>	26 (23; 31)	25 (22; 29)	26 (24; 33)	0.03
At inclusion				
SOFA score	15 (12; 18)	16 (13; 18)	14 (11; 18)	0.12
Weight, kg	80 (71; 97)	79 (65; 91)	80 (73; 98)	0.24
Height, m	1.72 (1.65–1.78)	1.70 (1.65–1.75)	1.75 (1.68–1.78)	0.18
ICU admission-to-ECMO interval, days	1 (0; 7)	1 (0; 5)	1 (0; 8)	0.52
ICU admission-to- $C_{\max}$ interval, days	9 (5; 15)	8 (3; 15)	9 (6; 15)	0.46
ECMO-to- $C_{\max}$ interval, days	6 (3; 11)	7 (1; 12)	6 (3; 9)	0.99
Inotrope score, $\mu\text{g}/\text{kg}/\text{min}$	30 (5; 131)	68 (10; 150)	21 (5; 105)	0.12
Reason for ECMO				
Cardiogenic shock	49 (46)	17 (41)	32 (49)	0.68
Post-cardiac transplant	9 (8)	3 (7)	6 (9)	
Cardiac arrest	7 (7)	2 (5)	5 (8)	
Post-cardiotomy	6 (6)	2 (5)	4 (6)	
Severe ARDS	35 (33)	17 (41)	18 (28)	
VA-ECMO	72 (68)	25 (61)	47 (72)	0.22
ECMO flow, L/min	4.0 (3.0; 5.0)	4.2 (3.2; 5.4)	3.7 (2.9; 4.6)	0.13
Weight-indexed ECMO flow, L/min/kg	0.49 (0.37–0.58)	0.53 (0.42–0.64)	0.46 (0.36–0.55)	0.013
ECMO-membrane duration, days	5 (2; 8)	4 (1; 8)	5 (3; 8)	0.16
Laboratory finding				
Aspartate aminotransferase, mmol/L	79 (41; 267)	99 (44; 747)	71 (39; 188)	0.08
Alanine aminotransferase, mmol/L	56 (27; 157)	69 (41; 377)	53 (25; 126)	0.08
Bilirubin, mmol/L	27 (16; 67)	23 (17; 66)	30 (15; 67)	0.92
Prothrombin time, %	65 (51; 77)	62 (43; 76)	66 (54; 78)	0.16
V factor, %	75 (47; 112)	59 (29; 107)	83 (57; 123)	0.08
Proteinemia, g/L	53 (43; 58)	49 (44; 55)	55 (48; 59)	0.02
Albuminemia, g/L	21 (19; 25)	22 (19; 25)	21 (19; 25)	0.86
Prealbuminemia, g/L	0.13 (0.09; 0.19)	0.13 (0.11; 0.19)	0.13 (0.09; 0.19)	0.65
Hematocrit, %	25 (23; 27)	24 (22; 27)	25 (23; 29)	0.09
Lactates, mmol/L	1.8 (1.2; 4.0)	1.9 (1.1; 6.3)	1.8 (1.3; 3.8)	0.89
Hemodilution parameter				
24-h fluid balance, mL	225 (–980; 1607)	1000 (200; 2045)	–371 (–1564; 1342)	< 0.001
24-h protidemia delta, %	0 (–5; 3.5)	0 (–5.6; 1.8)	0 (–3.9; 5.0)	0.37
24-h hematocrit delta, %	0.0 (–5.2; 3.5)	0.0 (–5.6; 1.8)	0.0 (–3.9; 5.0)	0.38
GFR, mL/min	2 (0; 69)	0 (0; 84)	6 (0; 61)	0.97
Renal function				
KDIGO-0	30 (28)	14 (34)	16 (25)	0.42
KDIGO-1	11 (10)	2 (5)	9 (14)	
KDIGO-2	6 (6)	2 (5)	4 (6)	
KDIGO-3	59 (56)	23 (56)	36 (55)	

**Table 1** Total population characteristics and univariable analyses of factors predictive of amikacin  $C_{max} < 60$  mg/L (Continued)

Characteristic	Total population (n = 106)	$C_{max} < 60$ mg/L (n = 41)	$C_{max} \geq 60$ mg/L (n = 65)	p
KDIGO $\geq 2$	65 (61)	25 (61)	40 (62)	0.95
Dialysis	9 (8)	1 (2)	8 (12)	0.07
CRRT	45 (42)	22 (54)	23 (35)	0.06
Outcome				
ICU mortality	57 (54)	21 (51)	36 (55)	0.67
Hospital mortality	58 (55)	21 (51)	37 (57)	0.57
ECMO duration, days	18 (10; 26)	18 (8.5; 24.5)	18 (10; 27)	0.83
Mechanical ventilation duration, days	22 (12; 41)	26 (17; 46)	20 (12; 38)	0.32
RRT duration after $C_{max}$ , days	15 (5; 24)	15 (4; 26)	14 (5; 21)	0.64
AKI <sup>b</sup> at ICU discharge in survivors <sup>c</sup>	11 (23)	5/20 (12)	6/29 (9)	0.65

AKI acute kidney injury, ARDS acute respiratory distress syndrome, BMI body mass index,  $C_{max}$  peak serum concentration CRRT continuous renal replacement therapy, GFR glomerular filtration rate, ICU intensive care unit, KDIGO Kidney Disease: Improving Global Outcomes, SAPS Simplified Acute Physiology Score, SOFA Sequential Organ-Failure Assessment, VA-ECMO venoarterial extracorporeal membrane oxygenation

<sup>a</sup>Values are expressed as median (1st; 3rd quartile) or number (percentage)

<sup>b</sup>Defined as KDIGO  $\geq 2$

<sup>c</sup>Based on 49 ICU survivors

Multivariable analyses retained BMI  $< 22$  kg/m<sup>2</sup> (OR, 6.38; 95% CI, 1.79–22.77;  $p = 0.043$ ) and 24-h fluid balance (OR per 500-mL increment, 1.28; 95% CI, 1.05–1.65;  $p = 0.041$ ) as being independently associated with a higher risk of  $C_{max} < 60$  mg/L. A linear relationship between the probability of amikacin  $C_{max} < 60$  mg/L and 24-h fluid balance was observed. That probability reached  $> 60\%$  when 24-h fluid balance exceeded 2000 mL (Fig. 2). Notably, we did not find any significant association between  $C_{max} < 60$  mg/L and ECMO settings (i.e. VA or VV), ECMO flow, and ECMO membrane duration.

#### Factors predictive of $C_{max} > 80$ mg/L

Univariable analyses selected higher BMI, ECMO flow, dialysis, and higher hematocrit as factors predictive of  $C_{max} > 80$  mg/L (Additional file 1: Table S3); 24-h-hour

fluid balance was forced into the logistic regression (Additional file 1: Table S1). Multivariable analyses retained only higher BMI (OR, 1.10; 95% CI, 1.03–1.18;  $p = 0.0037$ ) as being independently associated with a higher risk of  $C_{max} > 80$  mg/L.

#### Dosing simulations

Figure 3 describes the simulated  $C_{max}$  for various amikacin dosing regimens in a critically ill patient on ECMO with either a 24-h positive or negative fluid balance and a BMI  $<$  or  $\geq 22$  kg/m<sup>2</sup>. The probability of target attainment ( $C_{max}$  60–80 mg/L), under-dosing ( $C_{max} < 60$  mg/L) and overdosing ( $C_{max} > 80$  mg/L) is also reported. These data show that increasing amikacin doses up to 30 mg/kg for patient with a positive 24 h-fluid balance may increase the likelihood of reducing under-dosing. Based on dosing simulation, 28% of these patients still exhibit under-dosing with 30 mg/kg, whereas it will also expose the patient to more frequent overdosing (Fig. 3). In addition, increasing amikacin dosing regimen up to 30 mg/kg and 35 mg/kg TBW when 24-h fluid balance is positive and the BMI is  $\geq 22$  kg/m<sup>2</sup> or  $< 22$  kg/m<sup>2</sup> (Table 3), respectively, would have potentially led to the therapeutic target being reached in 42% of patients while reducing under-dosing incidence to 23% of patients (Additional file 1: Figure S2).

#### Outcomes

Overall in-ICU mortality was 54% after, respectively, 22 (12; 41) days on mechanical ventilation and 18 (10; 26) days on ECMO. Among ICU survivors, the 11 patients (23%) who suffered acute kidney injury (AKI) had comparable  $C_{max}$  levels to those without AKI (Table 2). No

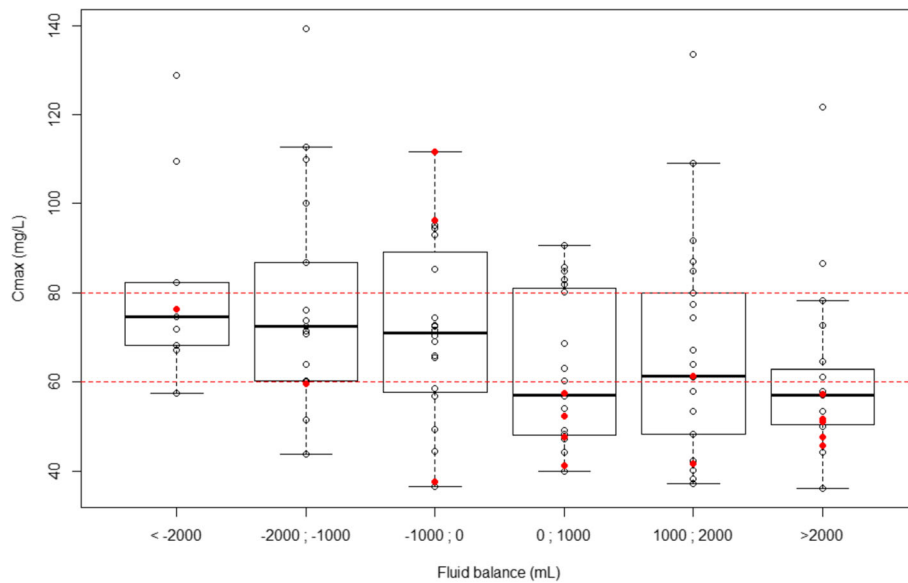
**Table 2** Pharmacokinetic/pharmacodynamic parameters at inclusion in 106 patients

Variable	Value <sup>a</sup>
Weight at time of $C_{max}$ , kg	80.0 (71.0; 97.5)
Amikacin dose, mg	2000 (1750; 2500)
Amikacin regimen, mg/kg	25.0 (24.0; 25.5)
Amikacin $C_{max}$ , mg/L	65.8 (51.8; 82.4)
Patients with $C_{max} < 60$ mg/L	41 (39)
Patients with $C_{max} > 80$ mg/L	27 (25)
ICU admission-to- $C_{min}$ interval, h	24.1 (23.4; 24.8)
Amikacin $C_{min}$ , mg/L	7.25 (3.60; 13.60)
Patients with $C_{min} < 2.5$ mg/L <sup>b</sup>	24 (28)

$C_{max}$  peak serum concentration,  $C_{min}$  trough serum concentration

<sup>a</sup>Values are expressed as median (1st; 3rd quartile) or number (percentage)

<sup>b</sup>Available for 85 patients



**Fig. 2** Amikacin peak serum concentration ( $C_{\max}$ ) after a single dose of 25 mg/kg total body weight according to 24-h fluid balance on extracorporeal membrane oxygenation (ECMO). Concentrations in patients with body mass index (BMI) < 22 kg/m<sup>2</sup> or > 22 kg/m<sup>2</sup> are represented by red dots and circles, respectively. Boxplots represent the distribution of the concentrations. The lower and upper borders correspond to the first and third quartiles. The upper whisker extends from the borders to the highest value that is within 1.5 \* interquartile range (IQR) of the borders, or the distance between the first and third quartiles. The lower whisker extends from the borders to the lowest value within 1.5 \* IQR of the hinge. Red dashed lines represent the therapeutic margin (60–80 mg/L)

association was found between ICU mortality and insufficient  $C_{\max}$  or too high  $C_{\min}$ . In addition, ICU mortality did not differ significantly in patients with  $C_{\max}$  < 60, 60–80, or > 80 mg/L (59%, 52%, or 51%, respectively).

## Discussion

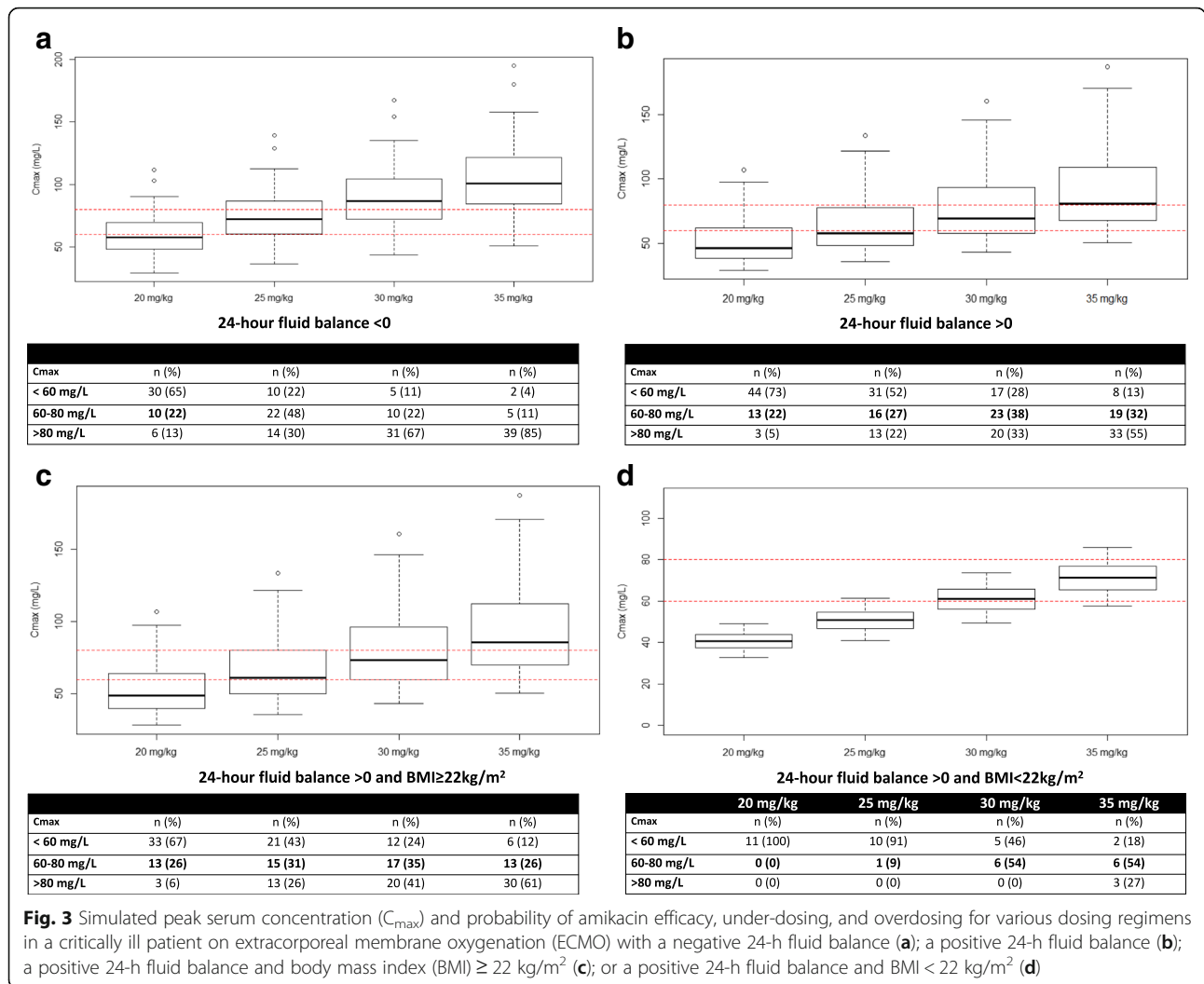
The results of our large prospective study indicate that amikacin under-dosing on ECMO after a loading dose of 25 mg/kg TBW is frequent, with more than a third of the patients having  $C_{\max}$  < 60 mg/L. In addition, using a 25 mg/kg amikacin dosing regimen led to 64% of patients with a  $C_{\max}$  outside the targeted range of 60–80 mg/L. Independent risk factors for amikacin under-dosing were BMI < 22 kg/m<sup>2</sup> and positive 24-h fluid balance, in agreement with previous studies without ECMO [17–20]. No association between under-dosing or overdosing of amikacin and outcome was found. Last, dosing simulations might suggest to increase the amikacin dosing regimen up to 30 mg/kg and 35 mg/kg TBW when 24-h fluid balance is positive and the BMI is > 22 kg/m<sup>2</sup> or the BMI is < 22 kg/m<sup>2</sup>, respectively.

Describing antibiotic PK in the population on ECMO is essential to understand whether special dosing may be required. Unfortunately, such data on ECMO-treated adults are sparse and the available literature is mainly restricted to ex-vivo studies [4, 6, 21]. Systemic inflammatory responses, organ dysfunction, drug interactions and organ support are all known to affect antibiotic PK in

critically ill patients. Drug PK seems to be more markedly modified on ECMO [6]. General PK parameters of hydrophilic antibiotics, like aminoglycosides, are low Vd, predominantly with renal clearance, and low intracellular penetration [22].

Recently, in a large case series of 146 severely ill patients receiving 181 amikacin infusions, including 15% on ECMO,  $C_{\max}$  was < 60 mg/L during 33% of the episodes. Independent risk factors were BMI < 25 kg/m<sup>2</sup> and positive 24-h fluid balance [11]. Although many factors, e.g. the extracorporeal circuit, high-volume fluid infusion and the extreme severity of critical illness in the patients could contribute to a larger Vd on ECMO, we found similar frequencies of amikacin under-dosing and overdosing with the same risk factors. Based on a smaller cohort of 46 ECMO-treated patients, Gelisse et al. reported a similar percentage of  $C_{\max}$  insufficiency, when matched with critically ill patients without ECMO support [5]. We postulate that, as demonstrated without ECMO [19–21], the intensity of interstitial fluid shift during sepsis on ECMO will result in a larger Vd, which might lower plasma antibiotic concentrations. It is worth noting that the increased Vd in septic patients may be attributed to hypoalbuminemia and the resulting decreased oncotic pressure [22], which was low in our population.

Low BMI (i.e. < 22 kg/m<sup>2</sup>) was the second independent risk factor for  $C_{\max}$  < 60 mg/L, which agrees with published observations [11, 12]. With hydrophilic drugs, like



amikacin, using TBW for dose calculation in high-BMI patients, instead of ideal body weight or adjusted body weight, could overestimate amikacin Vd. Indeed, higher BMI was the only factor that was independently associated with a higher risk of overdosing in our study. Surprisingly, although, a poor TBW–Vd relationship has been thoroughly described, the amikacin loading dose is still commonly adjusted to TBW. Therefore, we cannot rule out the fact that using adjusted body weight in obese patients [23] would have led to different findings.

Notably, Allou et al. [24] and Galvez et al. [25] reported, without a clear explanation, that amikacin overexposure (i.e.  $C_{max} > 80$  mg/L) might potentially be

**Table 3** Proposal for amikacin dosing regimens on ECMO according to 24-h fluid balance and body mass index (BMI)

	BMI < 22 kg/m <sup>2</sup>	BMI $\geq 22$ kg/m <sup>2</sup>
Negative 24-h fluid balance	25 mg/kg	25 mg/kg
Positive 24-h fluid balance	35 mg/kg <sup>a</sup>	30 mg/kg

<sup>a</sup>Based on only 11 patients with these characteristics

associated with increased mortality. Although, our study was not designed to analyze mortality, we did not observe any  $C_{max}$ –mortality association. Moreover, an amikacin  $C_{min} > 2.5$  mg/L was not significantly associated with a higher AKI rate at ICU discharge. Considering the high amikacin under-dosing frequency in our ECMO-treated patients and our dosing simulations, our dosing simulation suggests that increasing the loading dose up to a 35 mg/kg TBW dose for low-BMI patients and those with positive 24-h fluid balance on ECMO could help to obtain adequate target concentrations. However, these dosing simulations deserve to be confirmed by future prospective studies or Monte-Carlo-based simulations. Less frequent under-dosing has also been reported without a higher AKI rate, using a higher loading dose [24, 26]. However, despite the current trend toward increasing antibiotic doses in ICUs, no beneficial effect on outcome has been clearly demonstrated. In addition, it can be argued that a lower amikacin  $C_{max}$  might be enough to obtain  $C_{max}/MIC > 8$

for most isolated strains that often have amikacin MICs  $\leq$  4 mg/L [26].

Our study's strengths include the large cohort investigated, focusing on the impact of ECMO, its longitudinal design and a short interval retained for the correct time of  $C_{\max}$  determination. However, it also has limitations. First, it is a single-center study in an ICU with a high volume of ECMO cases in a tertiary-care university hospital, and our results may not be generalizable to all ICUs. Second, our ECMO population was a mix of patients who received VA-ECMO and VV-ECMO support, with different outcomes and underlying illnesses. Given that the underlying diseases of these extremely ill patients is key in antibiotic PK modifications on ECMO, our results might have been different if we had focused on a subpopulation of patients on ECMO (i.e. those with cardiac or respiratory failure). However, our multivariable analysis did not identify reasons for ECMO and type of ECMO hook-up as factors predictive of  $C_{\max}$  < 60 mg/L. Third, we cannot exclude that coadministration with another antibiotic and other ICU treatments might also have contributed to AKI at ICU discharge. Fourth, our dosing simulation was based on amikacin PK linearity [17–20] and a limited number of patients ( $n = 11$ ) with positive 24-h fluid balance and BMI < 22 kg/m<sup>2</sup>. And finally, we cannot rule out that a portion of amikacin might have been sequestered on the ECMO membrane, as previously described on the hemofilter membrane [27].

## Conclusions

Despite an amikacin loading dose of 25 mg/kg TBW in the ECMO-treated patients included in our large prospective study, we found that more than a third of them did not reach the targeted  $C_{\max} > 60$  mg/L. Increasing the dose to 35 mg/kg in low-BMI patients and those with positive 24-h fluid balance on ECMO to reach adequate targeted concentrations should be investigated. However, the impact of a higher amikacin loading dose on AKI frequency and outcomes remains unclear. Further human PK studies are urgently needed to confirm our results and develop population PK models to provide dosing guidelines for patients on ECMO.

## Additional file

**Additional file 1: Table S1.** List of the data included into the multivariable mixed models. **Table S2.** Infection sites, pathogens identified and their ECOFF for Amikacin in 88 patients with documented infections. **Figure S1.** Distribution of amikacin  $C_{\max}$  concentrations in ECMO-treated patients. **Table S3.** Total population characteristics and univariable analyses of factors predictive of amikacin  $C_{\max} > 80$  mg/L. **Figure S2.** Amikacin  $C_{\max}$  distribution within our population on ECMO with 25 mg/kg for all patients or with using potentially adapted dosing regimens based on 24-h fluid balance and BMI, as described in Table 3. (DOCX 273 kb)

## Abbreviations

AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; BMI: Body mass index;  $C_{\max}$ : Peak serum concentration;  $C_{\min}$ : Trough serum concentration; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; KDIGO: Kidney Disease: Improving Global Outcomes; MIC: Minimal inhibitory concentration; OR: Odds ratio; PK: Pharmacokinetics; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ-Failure Assessment; TBW: Total body weight; VA-ECMO: Venoarterial extracorporeal membrane oxygenation; Vd: Volumes of distribution

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

CT, NB, GF, GH, GL, SB, AN, and MS analyzed and interpreted the patient data. AA performed the pharmacodynamic analysis. PE performed pharmacokinetics simulations. CT, MS, PL, CEL, and AC were major contributors in writing the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study protocol was in accordance with the ethical standards of our hospital's Institutional Review Board (Committee for the Protection of Human Subjects). In accordance with French law, informed consent was not obtained for demographic, physiological and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies. However, patients and/or relatives were informed about the anonymous data collection and that they could decline inclusion. This database was registered at the Commission Nationale d'Informatique et des Libertés (CNIL, registration number 1950673).

## Consent for publication

In accordance with French law, informed consent was not obtained for demographic, physiological and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies. However, patients and/or relatives were informed about the anonymous data collection and that they could decline inclusion.

## Competing interests

Alain Combes has received lecture fees from Baxter and Gettinge and is the primary investigator of the EOLIA trial (NCT01470703), partly supported by Maquet-Gettinge. Matthieu Schmidt has received lecture fees from Gettinge and Dräger. The remaining authors have no conflicts of interest.

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