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## Amikacin in emergency surgery: how to dose it optimally?

**Running title:** Amikacin dosing in emergency surgery

Sylvain GOUTELLE<sup>A,b,c,\*</sup>, Guérin FRITSCH<sup>d</sup>, Marie LEROY<sup>a</sup>, Catherine PIRON<sup>a</sup>, Camille SALVEZ<sup>a</sup>, Pascal INCAGNOLI<sup>d</sup>, Jean-Stéphane DAVID<sup>d,e</sup>, Arnaud FRIGGERI<sup>e,f,g</sup>

<sup>a</sup> Hospices Civils de Lyon, Groupement Hospitalier Nord, Service de Pharmacie, Lyon, France

<sup>b</sup> Univ Lyon, Université Claude Bernard Lyon 1, CNRS UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, Villeurbanne, France

<sup>c</sup> Univ Lyon, Université Claude Bernard Lyon 1, ISPB – Faculté de Pharmacie de Lyon, Lyon, France.

<sup>d</sup> Hospices Civils de Lyon, Groupement Hospitalier Sud, Service d'Anesthésie-Réanimation, Pierre-Bénite, France

<sup>e</sup> Université Claude Bernard Lyon 1, Faculté de Médecine Lyon Est, Lyon, France

<sup>f</sup> UMR CNRS 5308, Inserm U1111, Centre International de Recherche en Infectiologie, Laboratoire des Pathogènes Émergents, Lyon, France

<sup>g</sup> Université de Lyon, Université Claude Bernard Lyon 1, Faculté de Médecine Lyon Sud-Charles Mérieux, Oullins, France

**\*Corresponding author:** Pr Sylvain Goutelle, Hospices Civils de Lyon, GH Nord, Hôpital Pierre Garraud, 136 rue du Commandant Charcot 69005 Lyon

**Email:** [sylvain.goutelle@chu-lyon.fr](mailto:sylvain.goutelle@chu-lyon.fr)

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### **Highlights:**

- 32% of patients who received amikacin for emergency surgery did not achieve the PK/PD target
- An amikacin dose  $\leq 21.5$  mg/kg was the primary predictor of failure to achieve the target
- The amikacin optimal dose varied widely, ranging from 770 mg to 4800 mg
- A fixed initial dose of 2500 mg of amikacin could simplify and optimise dosing

## **Abstract**

Amikacin is still a recommended option in emergency surgery. Current guidelines have suggested an amikacin dose of 15-20 mg/kg/24 h for intra-abdominal infections (IAI). Our objectives were to analyse amikacin pharmacokinetics (PK) and dosage requirements in patients who underwent emergency surgery, and to identify an optimal dosing approach.

We performed a retrospective data analysis of patients who received amikacin for emergency surgery over 2.5 years, with measurement of both peak ( $C_{max}$ ) and trough ( $C_{min}$ ) concentration after the first dose. The BestDose software was used to analyse amikacin concentrations and simulate various alternative dosage regimens in each patient. We compared concentration estimates with target values:  $C_{max} > 64$  mg/L and  $C_{min} < 2.5$  mg/L at 24 h. Classification and regression tree analysis was used to identify determinants of  $C_{max}$  target attainment (TA) and optimal dose.

Data from 84 patients, including 62 with IAI, were analysed. Despite a median initial dose of 25 mg/kg, 32% of patients did not achieve the  $C_{max}$  target. An amikacin dose  $\leq 21.5$  mg/kg was the primary predictor of failure to achieve the target. A dose of 30 mg per kg of total or corrected body weight, as well as a fixed dose of 2500 mg would result in the highest TA. The primary determinants of the optimal dose were ideal body weight, age, and renal function. To conclude, recommended dosages of amikacin in emergency surgery are not optimal. A fixed initial dose of 2500 mg could simplify and optimise dosing in this setting.

**Keywords:** amikacin, pharmacokinetics, emergency surgery, intra-abdominal infections

## Introduction

Aminoglycoside agents are recommended for antimicrobial prophylaxis in surgery, especially in patients with a beta-lactam allergy [1]. For example, they may be used as antimicrobial prophylaxis for urological procedures [2]. Amikacin is a recommended option for empirical therapy of healthcare-associated intra-abdominal infections (IAI) in both non-critically ill and critically ill patients, those being common surgical emergencies [3, 4]. Current guidelines suggest a dosage of 15-20 mg/kg every 24 h (q24) for amikacin in this indication [4].

Aminoglycosides are concentration-dependent antimicrobial agents. Pharmacokinetic/Pharmacodynamic (PK/PD) indices of efficacy are the ratio of the maximal concentration ( $C_{max}$ ) over the bacterial Minimum Inhibitory Concentration (MIC, and  $C_{max}/MIC$  ratio), and the ratio of the area under the concentration-time curve (AUC) over the MIC (AUC/MIC) [5, 6]. Target values of 8 to 10 and 80-100 have been suggested for amikacin  $C_{max}/MIC$  and AUC/MIC, respectively [7]. In addition, the trough concentration ( $C_{min}$ ) is considered as a predictor of nephrotoxicity, with a target value  $< 2.5$  mg/L for amikacin [7].

Achieving the PK/PD targets of efficacy with the first aminoglycoside dose is desirable in emergency surgery. However, there is little information about the ability of recommended dosage (15-20 mg/kg every 24 h) to achieve PK/PD targets in this setting, and alternatives to weight-based dosing have not been thoroughly investigated.

The objectives of the present study were to describe the pharmacokinetics (PK) and dosage requirements of amikacin in emergency surgery patients and to identify an optimal dosing approach.

## **1. Patients and methods**

### *1.1. Data collection*

We performed a retrospective data analysis of patients who received amikacin for emergency surgery and had Therapeutic Drug Monitoring (TDM) with measurement of both peak ( $C_{\max}$ ) and trough ( $C_{\min}$ ) concentration after the first amikacin dose. Antibiotic therapy was initiated as prophylaxis and/or probabilistic therapy during surgery, according to clinical guidelines. It could be discontinued after surgery when infection was not confirmed. The study was conducted in a 1000-bed hospital in France. Data were collected from December 2013 to June 2016. This was a non-interventional study and TDM was performed as part of routine patient care. In accordance with French laws, no informed consent nor ethics approval was required for conducting this analysis [8].

Data collected and used for PK analysis included drug doses, drug administration times, intravenous infusion times, blood sampling times, measured drug concentrations, as well as patients' sex, age, weight, serum creatinine and creatinine clearance. Microbiology data were also collected including site of infection and identified pathogen. Sampling for microbiology analysis was performed during and/or after surgery on various types of samples including urine, blood, and peritoneal fluid. Other demographic and clinical data were examined as potential predictors of amikacin optimal dose (see below).

## 1.2. PK analysis

All patients received amikacin administered as a 30-min intravenous (IV) infusion. Blood sampling for determination of amikacin  $C_{max}$  and  $C_{min}$  was done at approximately 30 min and 24 h after the end of the first infusion. Times were precisely recorded in each patient. Amikacin concentrations were determined by particle enhanced turbidimetric inhibition immunoassay (PETINIA) on a Siemens analyser. The limit of quantification of the method was 0.52 mg/litre. Maximum inter-day variability was 1.50% at mean concentrations of 4.62, 15.5, and 30.71 mg/litre.

We compared measured  $C_{max}$  and  $C_{min}$  to target values recommended. The conventional amikacin  $C_{max}$  target is 8-10 x MIC [7]. Considering a MIC breakpoint of 8 mg/L for *Enterobacterales* as defined by EUCAST ([https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Breakpoint\\_tables/v\\_11.0/\\_Breakpoint\\_Tables.pdf](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0/_Breakpoint_Tables.pdf)), this translates into a  $C_{max}$  target of 64-80 mg/L for initial dosing. Amikacin  $C_{min}$  target somewhat varies in the literature. We considered a target  $C_{min}$  < 2.5 mg/L in accordance with French and international guidelines [7, 9].

The BestDose software [10] was used to analyse amikacin concentrations in each individual patient. We performed Bayesian fitting of patients' data by using the amikacin model implemented in BestDose. This two-compartment model was based on a large population PK study conducted in 634 adult patients who received amikacin by intravenous or intramuscular route [11]. Individual Bayesian posterior PK parameters of amikacin and PK profile were estimated in each patient. Because the  $C_{max}$  and  $C_{min}$  samples were not obtained at the same exact time in all patients, the model was used to estimate amikacin  $C_{max}$  at 30 min post-dose and  $C_{min}$  at 24 h exactly. We also compared those  $C_{max}$  and  $C_{min}$  estimates to target values [7, 9].

Then, we used the BestDose software to calculate the optimal dose of amikacin that would have been required to achieve a target  $C_{max}$  of 64 mg/L, 30 min after a 30 min-infusion, in each patient. We also simulated various amikacin doses and assess their ability to achieve the target  $C_{max}$  of 64 mg/L. The dosages tested were 20, 25 and 30 mg per kg of total body weight (TBW), as well as 20, 25 and 30 mg per kg of corrected bodyweight (CBW). CBW definition was based on ideal body weight (IBW) and TBW. CBW was equal to IBW (IBW) when TBW was less than or equal to 20% of IBW. When TBW was greater than 20% of IBW, CBW was defined as follows:  $CBW = (IBW + 0.4*(TBW-IBW))$ , which is also known as adjusted body weight. This weight-based algorithm for aminoglycoside dosing is recommended by the State of Queensland, Australia [12]. IBW was estimated by the Devine's equation [13]. A fixed amikacin dose of 2500 mg was also evaluated, as suggested by White et al. [14].

### *1.3. Determinants of target attainment and optimal dose*

We performed exploratory regression tree analysis to identify determinants of the optimal dose of amikacin as computed by PK modelling. The Statistica software was used for this analysis (version 13.3, Tibco software, Palo Alto, CA, California). The following variables were evaluated as potential predictors of the optimal amikacin dose: age, sex, height, TBW, IBW, ratio of TBW over IBW, body mass index, body surface area (BSA), serum creatinine, creatinine clearance estimated by the Cockcroft-Gault equation ( $CL_{CR}$ ), blood urea nitrogen (BUN), ASA (American Society of Anesthesiologists) score, cardiac index, chronic renal failure, liver cirrhosis, diabetes, outpatient status, transfer from ICU to surgery, transfer to ICU after surgery, second surgery, digestive site of infection, volume of IV fluid administered during surgery, volume of blood loss and volume of other fluid loss. In order to prevent

overfitting, we set the minimal number of observations per node to 10 and performed a 5-fold cross validation of the final tree.

We also performed classification tree analysis to identify determinants of  $C_{\max}$  target attainment ( $\geq 64\text{mg/L}$ ) coded as a binary variable. The independent variables and settings were similar to those used in the regression tree analysis of optimal dose.

## 2. Results

Data from 84 patients were available for the analysis. Characteristics of the study population are shown in **Table 1**. Suspected infection of the abdomen or digestive tract was the most common indication ( $n = 62$ ). Nine patients were transferred from the ICU to the surgery unit, and 34 patients were transferred to the ICU after surgery. Microbiology data were available in 70 patients. In those patients, the pathogens identified were as follows: polymicrobial including Gram negative ( $n = 25$ ), Gram negative only ( $n=14$ ), polymicrobial without Gram negative ( $n = 5$ ), Gram positive only ( $n = 4$ ), anaerobes only ( $n = 2$ ). No pathogen was identified in 20 patients.

Ten-fold variability was observed in measured  $C_{\max}$  (range, 15.9 to 160.2 mg/L).  $C_{\min}$  estimated at 24 h was also highly variable (range, 0 to 46.7 mg/L). Despite a median dose of 25 mg/kg, 32% of patients did not achieve the  $C_{\max}$  target of 64 mg/L at 30 min post-dose. Amikacin  $C_{\min}$  at 24 h was higher than the target (2.5 mg/L) in 54% of patients.

The amikacin population model fitted the data ( $n = 168$  concentrations) well, as shown in the supplementary material. The median prediction error was -0.38 mg/L, and the median absolute prediction error was 11.5%. The equation of the regression line of predicted *versus*



observed amikacin concentrations was as follows:  $y = 0.89x + 1.62$ , with  $R^2 = 0.93$ . Very large variability was observed in PK parameter values, as shown in **Table 1**. Coefficients of variation of amikacin central volume of distribution ( $V_1$ ), clearance (CL) and half-life ( $T_{1/2}$ ) were 38%, 94%, and 63%, respectively.

The distribution of the individual optimal doses of amikacin calculated with the BestDose software is shown in **Figure 1**. The median optimal dose was 1450 mg, but varied widely between patients, ranging from 770 mg to 4800 mg. **Figure 2** shows the achievement of  $C_{max}$  ( $\geq 64$  mg/L) and  $C_{min}$  ( $< 2.5$  mg/L) targets for various simulated doses. A dose of 30 mg per kg of TBW or CBW was necessary to achieve the  $C_{max}$  target in more than 90% of patients. Interestingly, the fixed dose of 2500 mg was associated with target attainment rate comparable to that of those high weight-based doses. As expected, achievement of the  $C_{min}$  target decreased with increasing doses, but differences were small between dosages. The optimal doses provided the best compromise between  $C_{max}$  and  $C_{min}$  target attainment.

**Figure 3** summarises the determinants of the optimal dose identified by the regression tree algorithm. The correlation between optimal doses predicted by the tree and optimal doses computed by BestDose was moderate ( $R^2 = 0.53$ ). The primary predictor was IBW. The highest amikacin dose was identified in patients with  $IBW > 71.2$  kg and age  $< 63$  years, age being a secondary predictor. In patients with  $IBW \leq 71.2$  kg,  $CL_{CR}$  was a secondary predictor. In patients with augmented renal clearance ( $CL_{CR} > 129$  ml/min), the optimal dose was larger. BSA was a third predictor in patients with  $CL_{CR} \leq 129$  ml/min. Interestingly, TBW was not identified as a predictor of optimal amikacin dose.

In the classification tree analysis, amikacin dose  $\leq 21.5$  mg/kg (total body weight) was the primary predictor of failure to achieve the  $C_{max}$  target. The failure rate was 84% (21/25) in

patients who received a dose  $\leq 21.5$  mg/kg *versus* 10% (6/59) in patients who received more than 21.5 mg/kg. In this latter group, BUN was as secondary predictor.

### 3. Discussion

Optimal dosing of aminoglycosides remains challenging in clinical practice. In critically ill patients, several studies have described suboptimal rates of achieving a therapeutic amikacin peak concentration, despite the use of recommended dosages of 20 – 30 mg/kg [15-18]. In patients with sepsis and septic shock, an initial dose of  $\geq 25$  mg/kg was suggested by Taccone et al. [15]. TDM is recommended to control the exposure and adjust the dosage of aminoglycosides [7]. However, TDM cannot be performed to individualise the first dose.

Emergency surgery is a special situation of antimicrobial use. The treatment is always probabilistic, as the pathogen and its susceptibility have not been identified. Achieving PK/PD targets up to MIC clinical breakpoints after the first dose is desirable.

Our results showed large PK variability of amikacin in patients who underwent emergency surgery, most of them for IAI. About one-third of patients did not achieve the  $C_{max}$  target of 64 mg/L at 30 min post-dose, despite a median dosage of 25 mg/kg. This median dosage was higher than recommended, but the individual doses vary widely between patients (10 to 38 mg/kg). Low dosages ( $\leq 21.5$  mg/kg) were associated with poor target attainment. Overall, our results suggest that the dosage recommended in IAI (15-20 mg/kg q24 h [4]) is not optimal.

We explored the ability of various dosages in mg/kg of TBW, as well as alternative dosing approach to better achieve the  $C_{max}$  target. A higher dosage of 30 mg per kg of TBW or CBW

could improve  $C_{\max}$  target attainment. However, a fixed dose of 2500 mg may be as effective and would be simpler in clinical practice, as suggested elsewhere[14].

This study also confirms that efficacy and safety targets of aminoglycosides are conflicting, as 54% of patients showed  $C_{\min} > 2.5$  mg/L at 24 h in our study. This is in accordance with previous studies in critically ill patients [17, 19]. Based on our simulations, higher dosages would result in a potentially toxic  $C_{\min}$  that exceeds 2.5 mg/L 24 hours post-administration in many patients. The best way to minimise aminoglycoside  $C_{\min}$  is to perform TDM after the first dose and consider a dosage interval  $> 24$  h if necessary.

We identified an initial dose that would have optimised target attainment for both  $C_{\max}$  and  $C_{\min}$ . However, this dose was based on TDM results and cannot be precisely determined *a priori*. Several predictors of the individual optimal dose of amikacin were identified, including IBW, age, and renal function. Interestingly, total body weight was not a predictor of amikacin optimal dose, which supports the need for alternative dosing approaches [20]. The determinants identified may be considered in future studies on amikacin personalised dosing.

This study has several limitations. As it was performed as part of routine clinical practice, errors may have occurred in data collection. Regarding the classification and regression tree analysis of optimal dose and  $C_{\max}$  target attainment, we performed cross-validation because of the limited sample size. External validation would be interesting to confirm our findings. Of note, the goal of this exploratory CART analysis was to identify variables that discriminated patients' subgroups in terms of target attainment and optimal dose, not to build a robust predictive model. Also, the determinants identified in the CART analysis are

not validated for dosage guidance. Finally, the alternative dosing approaches identified are based on PK modelling and require further clinical evaluation.

#### **4. Conclusion**

This study suggests that current dosage guidelines for amikacin in emergency surgery are not optimal, as they are associated with insufficient  $C_{\max}$  target attainment. An initial amikacin dose of 2500 mg could optimise  $C_{\max}$  target attainment and should be further evaluated clinically in emergency surgery. A dosage interval of 24 h is too short for achieving target  $C_{\min}$  in many patients. TDM remains necessary after the initial dose to individualise both the dose amount and the dosage interval if aminoglycoside therapy is still required.

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#### **Conflicts of interest**

The authors have no conflicts of interest that are relevant with the content of this study.

**Table 1. Characteristics of the study population**

Variable	Value
Number of patients (number of women/men)	84 (36/48)
Age (years)	64 (17-88)
Total body weight (kg)	68 (35-120)
Corrected body weight (kg)	62 (35-95)
Body Mass Index (kg/m <sup>2</sup> )	25 (13-44)
CL <sub>CR</sub> (mL/min)	79 (6-274)
Suspected site of infection	
Abdomen or digestive tract (n)	62
Skin and soft tissues (n)	8
Urinary tract (n)	8
Other (n)	8
Amikacin initial dose (mg)	1750 (750-3000)
Amikacin initial dose (mg/kg)	25 (10-38)
Measured C <sub>max</sub> (mg/L)	77.3 (15.9-160.2)
Estimated C <sub>max</sub> at 30 min (mg/L)	72 (22-134)
Estimated C <sub>max</sub> at 30 min ≥ 64 mg/L (%)	68%
C <sub>min</sub> at 24h (mg/L)	3.3 (0 - 46.7)
C <sub>min</sub> at 24h < 2.5 mg/L (%)	46%
Amikacin V <sub>1</sub> (L/kg) <sup>a</sup>	0.24 (0.13 – 0.66)
Amikacin CL (ml/min) <sup>a</sup>	46.4 (4.8 – 367.4)
Amikacin T <sub>1/2</sub> (h) <sup>a</sup>	2.5 (1.7 – 10.3)

Values are given as median (min-max) unless otherwise stated.

<sup>a</sup> Those parameters were estimated by using the pharmacokinetic model (Bayesian posterior estimates).

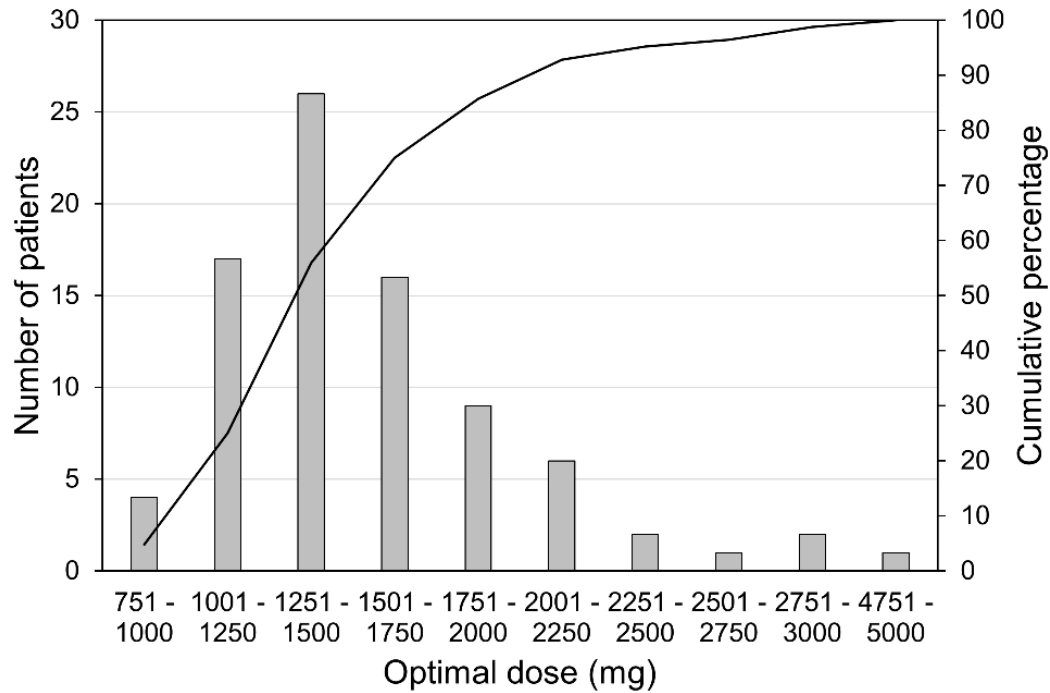
Abbreviation: CL, amikacin clearance; CL<sub>CR</sub>, creatinine clearance; C<sub>max</sub>, maximal concentration; C<sub>min</sub>, trough concentration; T<sub>1/2</sub>, half-life; V<sub>1</sub>, central volume of distribution.

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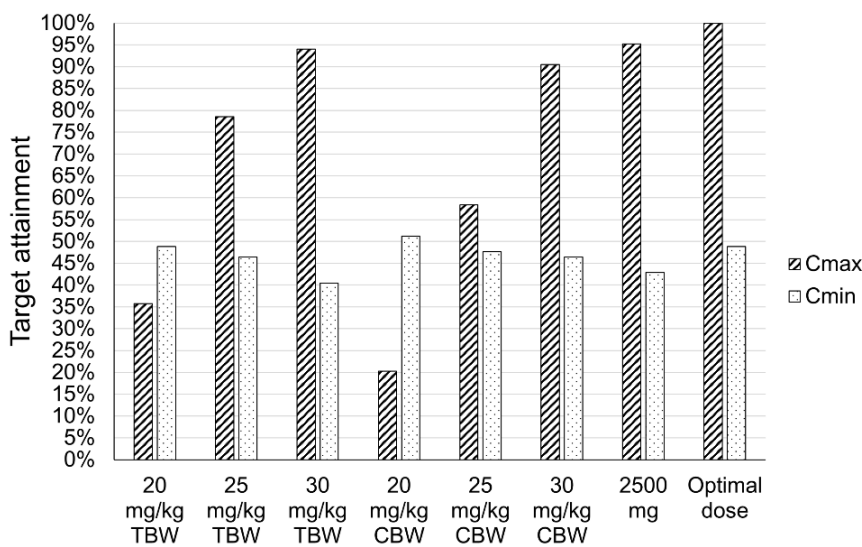
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**Figure 1:** Distribution of optimal amikacin doses estimated by PK modelling



Abbreviations: CBW, corrected body weight (see main text);  $C_{max}$ , maximal concentration,  $C_{min}$ , trough concentration at 24h; TBW, total body weight

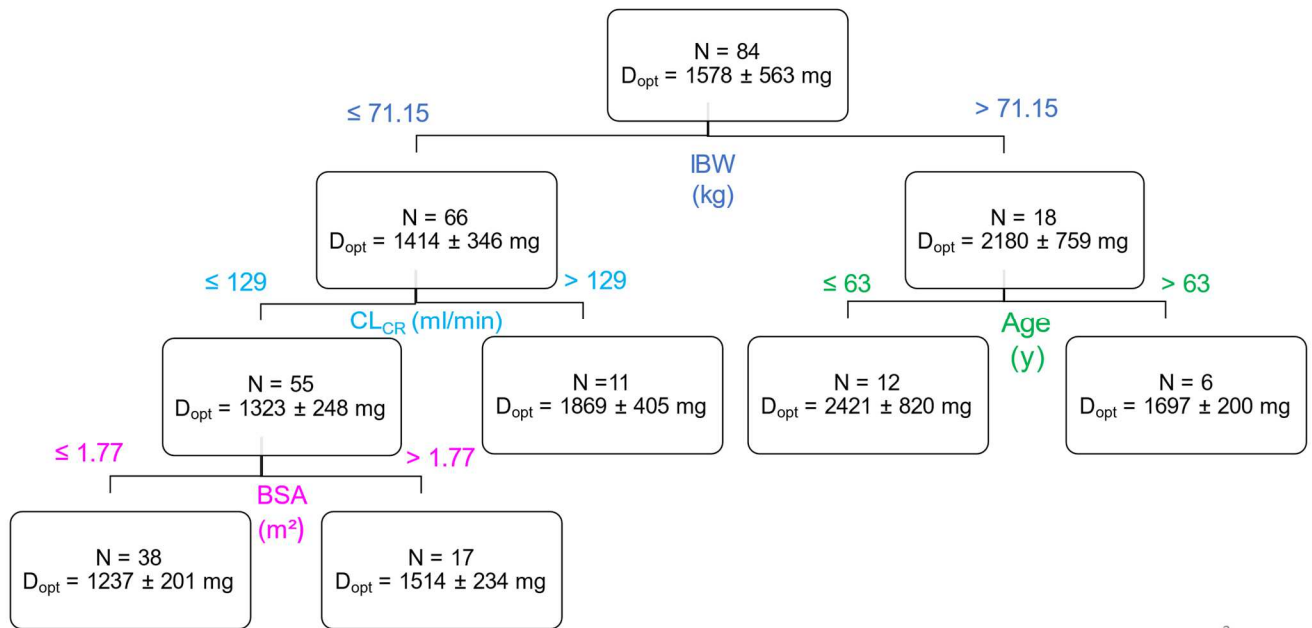
**Figure 2:** Attainment of  $C_{max}$  ( $\geq 64$  mg/L) and  $C_{min}$  ( $< 2.5$  mg/L) targets for various simulated dosages of amikacin



Abbreviations: CBW, corrected body weight (see main text);  $C_{max}$ , maximal concentration,  $C_{min}$ , trough concentration at 24h; TBW, total body weight



**Figure 3:** Regression tree of determinants of the optimal amikacin dose



Abbreviations: BSA, body surface area; CL<sub>CR</sub>, creatinine clearance; D<sub>opt</sub>, optimal amikacin dose; IBW, ideal body weight; y, years