

Aminoglycosides in the intensive care unit: What's new in population PK modeling?

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Abstract

Background Although aminoglycosides are often used as treatment for Gram-Negative infections, optimal dosing regimens remains unclear, especially in ICU patients. This is due to a large between- and within-subject variability in the aminoglycosides' pharmacokinetics in this population.

Objective The review provides comprehensive data on the pharmacokinetics of aminoglycosides in patients hospitalized in ICU by summarizing all published PopPK models in ICU patients for amikacin, gentamicin, and tobramycin. The objective was to determine the presence of a consensus on the structural model used, significant covariates included, and therapeutic targets considered during dosing regimen simulations.

Methods A literature search was conducted from the Medline/PubMed database, using the terms: 'amikacin', 'gentamicin', 'tobramycin', 'pharmacokinetic(s)', 'nonlinear mixed effect', 'population', 'intensive care' and 'critically ill'.

Results Nineteen articles were retained where amikacin, gentamicin and tobramycin pharmacokinetics were described in six, eleven and five models, respectively. Two-compartment model best described amikacin and tobramycin pharmacokinetics, whereas one-compartment model majorly described gentamicin pharmacokinetics.

The most recurrent significant covariates were renal clearance and bodyweight. Across all aminoglycosides, mean interindividual variability in clearance and volume of distribution were 41.6% and 22.0%, respectively. A common consensus for an optimal dosing regimen for each aminoglycoside was not reached.

Conclusion This review showed models developed for amikacin, from 2015 until now and for gentamicin and tobramycin from the past decades. Despite growing challenges of external evaluation, the latter should be more considered during model development. Further research including new covariates, additional simulated dosing regimens and external validation should be considered to better understand aminoglycosides pharmacokinetics in ICU patients.

1. Introduction

Aminoglycosides are a class of antibiotics used as treatment for Gram-negative infections in patients hospitalized in intensive care units (ICUs). Life-threatening infections, often caused by Gram-Negative bacteria[[1](#), [2](#)], may lead to pathophysiological conditions, such as sepsis, influencing the pharmacokinetics (PK) of many drugs including antibiotics [[3](#)]. For example, ICU patients may exhibit increased volume of distribution causing lower aminoglycosides peak concentrations [[4](#)]. Therefore, the selection of both the appropriate antimicrobial therapy and its respective dosage are essential for clinical cure [[5](#)]. As aminoglycosides follow concentration-dependent pharmacodynamics, the achievement of a peak concentration (C_{max}) over minimum inhibitory concentration (MIC) ratio greater than 10 is warranted for a clinical response [[6](#)]. Although the C_{max} /MIC target is primarily used in clinical situations due to its simplicity, multiple studies have shown that the area under the curve (AUC) to MIC ratio greater than 80-100 is the better pharmacokinetic/pharmacodynamic (PK/PD) indicator for efficacy [[6-8](#)]. Considering aminoglycosides' narrow therapeutic index with potential nephrotoxicity and ototoxicity, therapeutic drug monitoring (TDM) has been used to achieve these targets while minimizing toxicity by individualizing treatments [[9](#)]. This practice is especially crucial in ICU patients that suffer from septic shock where the survival rate is increased with the timely administration of an appropriate antibiotic [[10](#)].

In recent years, antibiotic dosing regimens have been developed with the help of population pharmacokinetic (PopPK) modeling and simulation [[11](#)]. Multiple studies have established PopPK models to characterize PK parameters and to gain a better understanding of the variability of aminoglycosides' clinical response based on ICU patients' characteristics. These studies have used nonlinear mixed effects modelling to target and quantify the contribution of specific demographic and pathophysiological characteristics that may influence the aminoglycosides' PK profile. This modelling method has been considered as one of the principal approaches in PopPK modeling due to the possibility of having sparse data for each subject while evaluating residual and interindividual variabilities [[12](#)]. Moreover, PopPK models can also be used to develop dosing recommendations by simulating several dosing regimens based on different PK/PD targets. However, it is also important to assess the validity of these models and the efficacy of the dosing recommendations in actual clinical settings in large populations. Generally, clinical

pharmacokinetic studies must present several key items to better ensure transparency in the reporting of the results[13].

The aim of this review is to provide comprehensive data on the pharmacokinetics of aminoglycosides in patients hospitalized in ICU by summarizing all published PopPK models in ICU patients for amikacin, gentamicin, and tobramycin.

2. Data sources

2.1. Search Strategy

A literature search was conducted from the Medline/PubMed database, from its inception until March 2020, using the following terms: *(amikacin OR gentamicin OR tobramycin) AND [(pharmacokinetics/ or renal elimination/) OR (pharmacokinetic* OR ((pharmaco OR drug) ADJ kinetic*)) OR area under curve? OR AUC OR (renal ADJ (elimination? or excretion? or clearance?))) OR (((nonlinear OR non-linear) ADJ mixed effect model*) OR NONMEM OR WinNonMix OR P-PHARM OR NLMIXED OR ADAPT)] AND (EXP population/ OR population groups/ OR (population? OR ethnic group?)) AND [critical care/ OR intensive care or EXP intensive care units/ OR critical illness/ OR ((intensive OR critical) ADJ care?)) OR ICU OR ((respiratory OR coronary) ADJ care unit?) OR (critical* ADJ (ill OR illness? OR disease?))].* Additional relevant studies were manually screened from the reference list of selected articles. The phases of systematic review are displayed in a flowchart (Figure 1), as described by the PRISMA 2009 statement for reporting systematic reviews and meta-analyses [14]. The research strategy was completed by two authors and cross-verification was performed.

2.2. Inclusion Criteria

Eligible studies had to meet the following inclusion criteria: (1) the article described a population pharmacokinetic model; (2) the treatment was either intravenous amikacin, gentamicin or tobramycin; (3) the studied population consisted of ICU adult patients; and (4) the article was published in the English language.

2.3. Exclusion Criteria

We excluded articles from this review if they met the following criteria: (1) a non-compartmental approach was used; (2) the studied population was composed of only cystic fibrosis patients; (3) the studies were published before 2015 for amikacin (this review served as an update to the amikacin review by Marsot et al. [15]; or (4) they were review articles.

2.4. Data Extraction

The following information were extracted from relevant articles : first author, year of publication, population characteristics (number of males and females, age, bodyweight, height and body mass index), study design, dosage regimen, sample collection (samples per patient, total samples and sample frequency), population PK modeling methods (Software used, model and evaluation method used), the formula of PopPK structural and statistical models, PK parameters, as well as tested and retained covariates. The model evaluation methods were divided into basic internal (goodness-of-fit plots), advanced internal (bootstrap resampling, Monte Carlo simulations, visual predictive check, normalized prediction distribution error, etc.) and external evaluation. This step was done by two authors and cross-verification was performed to ensure the accuracy of information extracted. Data extraction was based on the several items presented in the checklist created by *ClinPK* [13], as per [Table S1](#).

3. Data analysis

3.1. Study selection

A total of 78 studies were identified through the Medline/PubMed database, of which there were 26 articles for amikacin, 38 for gentamicin and 14 for tobramycin. After assessing the articles for eligibility by applying the inclusion and exclusion criteria, 19 publications were selected. In total, 6, 11, and 5 PopPK models were analyzed for amikacin [16-21], gentamicin [21-31] and tobramycin [32-34], respectively ([Figure 1](#)).

3.2. Population characteristics

The characteristics of the population studies are presented in [Table 1](#). Mean population age from these studies ranged from 32 years [34] to 74 years [31] with mean bodyweight ranging from 51 kg [25] to 92.5 kg [27].

3.3. Study designs and protocols

In [Table 1](#), among the 19 publications across all three aminoglycosides, the number of retrospective and prospective designs were similar, with ten and eight, respectively. another study had both retrospective and prospective designs [23]. Patients were mostly administered aminoglycosides through intravenous infusion with only two studies including intravenous bolus administration. The number of patients included ranged from 14 [27] to 208 [34]. Also, seven studies included less than 30 patients in their PopPK analysis [17, 20, 21, 27, 28, 31]. The number

of total samples and blood samples collected per patient varied across all studies for all three aminoglycosides. Peak and trough samples were usually the samples collected for studies following a TDM protocol (n=14) whereas a complete PK profile of the aminoglycoside was required for PK studies (n=5).

Amikacin was mostly administered following a once-daily dosing regimen in six respective study protocols, except for one where it was unknown but it was mentioned that dosing regimen followed establishment's standards [18]. For amikacin, the actual doses administered to the study populations ranged from 23 mg/kg/day to 41 mg/kg/day. Similarly, gentamicin dosing regimens were mostly once-daily administration. One prospective study administered three different dosing intervals to their study population: once-daily, twice-daily and thrice-daily [25], whereas another prospective study administered five different dosing intervals ranging from twice-daily to once every three days [30]. For all gentamicin studies, the daily dosage regimens as well as the actual administered doses were similar, ranging from 3 mg/kg to 7 mg/kg. Similarly, tobramycin was also given following a once-daily administration with dosing regimens and actual administered doses ranging from 5 mg/kg/day to 7 mg/kg/day.

3.4. Population Pharmacokinetic Analysis

All 19 studies included in this review used nonlinear mixed effect methods to analyze their data and develop PopPK models. As per Table 2, a version of NONMEM software was used for the modeling in more than half of the studies (n=10) [19, 22-27, 32-34]. Other software used were NPAG a function from the software Pmetrics (n=2) and the NPEM software (n=2). For model evaluation, more than half of these studies only used advanced internal evaluation, such as the bootstrap resampling method (n=10), three studies used both advanced internal and/or external evaluation with several external subjects ranging from 13 to 32 [19, 29, 33]. Tobramycin pharmacokinetics was described by a two-compartment model (n=3) [32-34], while amikacin and gentamicin pharmacokinetics were described by single-compartment (amikacin n=1 [19], gentamicin n=7 [23-25, 28-31]) and two-compartment models (amikacin n=5 [16-18, 20, 21], gentamicin n=4 [22, 26, 27, 21]).

3.5. Estimated Parameters

The mean estimated clearances (CL) were comparable across aminoglycosides whereas the mean volume of distribution (Vd) was slightly higher in amikacin compared to gentamicin and tobramycin. As per [Figure 2](#), the median values (range) of CL were 3.7 L/h (2.0 – 7.1 L/h), 3.0 L/h (1.15 – 5.7 L/h) and 3.95 L/h (3.14 – 7.23 L/h) across all studies for amikacin, gentamicin and tobramycin, respectively, whereas the median values (range) of Vd were 34.9 L (20.3 – 46 L), 29 L (19 – 53 L) and 35 L (30 – 53 L) for amikacin, gentamicin and tobramycin, respectively. CL and Vd values are also presented per study in [Table S2](#) and [Table S3](#) for single and bi-compartmental models, respectively.

3.6. Random effect modeling

Interindividual variability (IIV) for the main PK parameters was estimated only in a third of the amikacin studies [\[18, 19\]](#), whereas it was estimated in seven out of the 11 gentamicin studies [\[22-28\]](#). For tobramycin, all five studies estimated IIV for both CL and Vd [\[24, 28, 32-34\]](#). For amikacin, the median (range) values of IIV in CL and Vd (or Central Volume) following the inclusion of covariates were 47.0% (27.2% - 58.7%) and 33.6% (21.7% - 43.3%), respectively (n=3 for each parameter) [\[18, 19\]](#), with one study expressing IIV as ω^2 (variance of eta) [\[18\]](#). As for gentamicin, the median (range) values of IIV in CL and Vd (or Central volume) following the inclusion of covariates were 47.0% (29.3% - 83.7%) and 17.2% (11.9 - 64.4%), respectively (n=8 and 7 for CL and Vd, respectively) [\[24, 28, 32-34\]](#). For tobramycin, the median (range) values of IIV in CL and Vd (or Central Volume) following the inclusion of covariates were 30.8% (25.9% - 83.7%) and 15.2% (3% - 64.4%), respectively (n=5 for each parameter) [\[24, 28, 32-34\]](#). However, the highest IIV values for both CL and Vd were taken from a study that collected both gentamicin and tobramycin samples in their study population [\[24\]](#).

Across all aminoglycosides, the studies tested additive (n=2) [\[19, 28\]](#), proportional (n=6) [\[18, 22, 27, 32-34\]](#) or mixed error (additive and proportional) (n=5) [\[20, 23-26\]](#) models in order to determine residual variability. As per [Table S2](#) and [Table S3](#) in the Supplementary Information, for amikacin, residual variability was estimated using a proportional model (n=1) [\[18\]](#), an additive model (n=1) [\[19\]](#) and a mixed model (n=1) [\[20\]](#). As for gentamicin, the median (range) residual variability using a proportional model was 27.3% (20.8 – 33.8) (n=2) [\[22, 27\]](#) [\[27\]](#), whereas the

residual variability was estimated using an additive model in a single study where both gentamicin and tobramycin samples were used in the model development [28]. The median (range) using a mixed model were 24.3 % (19.4% - 32%) and 0.056 mg/L (3.81×10^{-4} mg/L – 0.13 mg/L) (n=3) [24-26]. Another study presented the residual variability estimated with a mixed model as variance [23]. For tobramycin, the median (range) residual variability using a proportional model was 21% (20.4% - 23.7%) (n=3) [32-34].

3.7. Inclusion of covariates

Table 3 summarizes the tested and significant covariates. For estimated clearance (CL), the most common retained covariate was creatinine clearance calculated using the Cockcroft-Gault (CG) equation (n=8) [16, 18-20, 23, 25, 32, 33]. Moreover, multiple covariates related to weight (total bodyweight (TBW) [17, 29], ideal bodyweight (IBW) [22] and lean bodyweight [27]) and body size (height [32] and free fat mass [34]) were also included (n=1, for each). Other retained covariates for CL were glomerular filtration rate [24], sex, serum creatinine and age [34], usage of renal replacement therapy (intermittent hemodialysis [23] or continuous venovenous hemofiltration (CVVH) [22]) and the inverse of the final plasma creatinine concentration recorded in $\mu\text{mol/L}$ before commencement of extended daily diafiltration (EDD-f) [27]. For the estimated Vd, most common retained covariates were related to weight and body size (body surface area (n=1) [16], adjusted bodyweight (n=1) [18], bodyweight (n=1) [24], ideal bodyweight (n=1) [22] and free fat mass (n=1) [34]). Other retained covariates for Vd were albumin [22] and sex [34], (n=1 each).

3.8. Simulation of dosing regimens

As per **Table 2**, amongst the nineteen articles selected in this review for all three aminoglycosides, twelve [Amikacin (n=4), Gentamicin (n=5) and Tobramycin (n=3)] of them simulated optimal dosing regimens in their respective population with various therapeutic targets [16-19, 23-27, 32-34]. All twelve studies included at least a target related to C_{\max} , while half of them also included a target related to AUC_{0-24} or AUC_{0-48} and five studies added trough concentration as one of their therapeutic or toxicity targets. Generally, dosing regimens simulated across studies were similar for all three aminoglycosides, with some adjustments based on the populations' characteristics. Many studies used various targets for their simulations. For amikacin, principal PK/PD targets were $C_{\max}/\text{MIC} \geq 8$, $AUC_{0-24}/\text{MIC} \geq 75$ and $C_{\min} \leq 2.5 \text{ mg/L}$ [16-18]. For gentamicin, main PK/PD

targets were C_{max}/MIC between 8 and 10, considering a MIC ranging from 1 to 2 mg/L [23-27]. As for tobramycin, C_{max} were targeted to be within 6 mg/L and 20 mg/L considering a MIC of 1 to 2 mg/L and C_{min} were to be ≤ 1 mg/L [32-34]

4. Discussion

To treat severe infections, administration of aminoglycosides in special populations have led to an increase of interest in aminoglycosides pharmacokinetics. Noticeably, considerable amount of PopPK models have been developed for ICU patients in the last decade [16-20, 22, 25-27, 29, 32, 34]. The 19 articles presented in this review exhibit many resemblances but also differences on the covariates included, the structure of the model and the simulation of dosing regimens. Studies presenting a design with TDM samples or a sparse sampling schedule were mostly associated with single-compartment models (n=8), whereas full profile sampling partially led to bi-compartment models (n=11). In fact, Marsot et al. suggested in their review that single-compartment models could lead to an inaccurate estimation of aminoglycosides Vd [15]. Although median CL and Vd values were comparable across aminoglycosides, as shown in Figure 2, the parameters values tended to vary from a study to another for each drug. As described previously, ICU patients are prone to present additional comorbidities, such as cardiovascular dysfunction, sepsis, burns or use of vasopressors and/or develop complications, like acute kidney injury (AKI) or conversely augmented renal clearance (ARC). Although ARC is expected to be present in 20-65% of critically ill patients [35], it was only considered in a few studies in this review [16, 18, 19, 25]. These complications usually lead to divergence in PK values as compared to healthy patients [36]. As per Figure 2a, based on similar dosing regimen, median CL for all three drugs in this present study were generally lower as compared to values in healthy volunteers; 6.48 L/hr, 4.03L/hr and 7.02 L/hr for amikacin, gentamicin and tobramycin, respectively [37-40]. As shown in Figure 2b, the median Vd values for all three drugs in this review were higher than values showed in healthy volunteers : 16.15 L, 13.3L/70kg and 20 L/70 kg for amikacin, gentamicin and tobramycin, respectively [37-40].

4.1. Major covariates

In addition of the changes due to critical illness, ICU patients may present other physiological characteristics potentially impacting aminoglycosides pharmacokinetics. To better understand the

inter- and intra-variability of aminoglycosides pharmacokinetics, these following covariates were the most retained in PopPK models: bodyweight (n=7), renal clearance (n=8).

4.1.1. Renal function

Amongst the twelve studies with normal renal function patients that performed a covariate analysis, seven studies included CL_{CR} calculated with Cockcroft-Gault equation (CL_{CG}) in order to better estimate values of CL or Vd [16, 18, 19, 23, 25, 32, 33]. To illustrate the impact of CL_{CR} on aminoglycosides CL, we plotted aminoglycosides CL against this covariate according to the values and model equations reported by the studies that included CL_{CR} (Figure 3). This plot showed how differences in CL_{CR} caused important variations in aminoglycosides CL within the same study group. Considering that the CL_{CG} includes the age, total bodyweight, and sex of an individual, these variables are thereby also considered in the estimation of aminoglycosides CL or Vd.

Although CL_{CG} seems to be frequently used in guidelines [41], it might not represent the most accurate way of estimating aminoglycosides clearance [42]. In fact, CL_{CG} is known to overestimate the CL_{CR} in underweight individuals [43]. As for obese individuals, the usage of CL_{CG} with IBW tends to underestimate the CL_{CR} , while the usage of TBW overestimates the CL_{CR} [43]. Many studies have been suggested that CL_{CG} shouldn't be used in intensive care settings [44-47]. Moreover, since CL_{CR} considers glomerular filtration as well as tubular secretion [48], measurements of GFR have been suggested to be a more precise estimate of aminoglycoside clearance [49]. In fact, aminoglycosides' elimination pathway is mainly by glomerular filtration, while tubular secretion and reabsorption are minimal, even when GFR levels are low. Zarowitz et al. compared gentamicin and tobramycin clearances to inulin (GFR), and CL_{CG} and their results showed a better linear regression between inulin and GFR ($R^2 = 0.93$) compared to a linear regression between inulin and CL_{CG} ($R^2 = 0.76$) [49]. Moreover, Lim et al. also compared different estimators of GFR with the traditional CL_{CG} and they determined that the best predictor of aminoglycoside clearance would be the estimation of glomerular filtration rate by CKD-EPI adjusted for BSA [41]. Considering the high prevalence of CL_{CG} among the studies included in this review and its frequent usage in dosing guidelines, the better estimator between CL_{CG} and GFR, in terms of accuracy and efficacy in clinical settings, is still debatable.

4.1.2. Bodyweight and body size

Since aminoglycosides are administered following a weight-based dose, the selection of the right weight parameter is essential to avoid overestimating or underestimating the dose needed. For example, in overweight patients, it is recommended to use an adjusted bodyweight that will consider a fraction of the excess bodyweight (total bodyweight - ideal bodyweight)[43]. Obesity is associated with major physiological changes such as an increased Vd for antibiotics, like aminoglycosides [50]. Therefore, administration of higher doses to reach targeted serum concentrations is needed. In several studies presented in this review, patients' weight was determined significant in the estimation of amikacin and gentamicin clearances (n=3) [17, 22, 27] and volume of distribution (n=3) [19, 22, 24]. To illustrate the impact of bodyweight in general on aminoglycosides Vd, the latter was plotted against this covariate according to the values and model equations reported by the studies that included a BW variable (Figure 3). Variations within BW from a same study seem to imply changes in aminoglycosides Vd. As mentioned earlier, bodyweight also has an influence on the estimation of the CL_{CR}, especially if CL_{CG} is used. All seven studies that included CL_{CG} in their final PopPK model used TBW in the CG equation [16, 18, 19, 23, 25, 32, 33]. For studies that included impaired renal patients, each study retained a bodyweight parameter in one of the two parameters their final model [17, 19, 22, 27]. Indeed, the inclusion of a bodyweight parameter is expected in this population considering that bodyweight is used in order to determine dialysate or ultrafiltration flow rate for renal replacement therapy (RRT) [17, 22, 23, 27].

For body size parameters, only body surface area (BSA), lean body mass according to the equation of Chennavasin (LBMc) and free fat mass (FFM) were retained covariates, respectively in amikacin, gentamicin and tobramycin models [16, 29, 34]. In fact, these three covariates were retained in the estimation of aminoglycosides Vd. Although BSA has been rarely mentioned as a covariate influencing aminoglycosides PK, it was suggested by Boidin et al. that the use of BSA might lower the risk of exposure in overweight patients [16, 51]. In fact, BSA considers both the bodyweight and height, where the latter is much less variable than bodyweight in ICU adult patients [52]. Recent studies did suggest dose recommendations based on height (mg/cm) instead of bodyweight-based dosing for tobramycin in cystic fibrosis patients [53, 54].

Although the inclusion of parameters related to bodyweight or body size in the final model of most studies has allowed a reduction of IIV, the latter remains relatively high across studies. This

variability could be explained by the inaccuracy and variability of the estimation of TBW or actual bodyweight of ICU patients [55, 56].

4.1.3. Age

The mean (range) age across all studies is 57.1 (31.7 - 73.8) years old [31, 34]. Although age was tested as a covariate in multiple studies, there was only a single study where it was retained in final PopPK model [34]. However, as mentioned previously, the CL_{CR} calculated CG includes multiple covariates such as age, which could explain why the latter hasn't appeared as a distinct covariate. In fact, this study included cystic fibrosis (CF) and non-CF infants, children, and adults under tobramycin treatment. While the presence of CF was not significant for any PK parameters, age was a significant factor when evaluating tobramycin clearance. In fact, its clearance increased by 2.1% per year from 2 to 18 years and declined by 1% for each following year [34]. It is known that kidney function in children is highly reduced due to the constant growth and maturation of both kidneys until adult age [57].

Although age was not a significant covariate in the estimation of aminoglycoside PK parameters in ICU patients, except when considered in the CG equation, an advanced age is often associated with several physiological changes such as loss of kidney function and modifications in body composition influencing drug absorption and distribution of drugs [58]. In fact, it has been suggested, that gentamicin renal clearance seemed to decline more significantly after reaching 60 to 70 years of age [59]. However, it was also mentioned that this decrease in gentamicin clearance might also be caused by other underlying diseases. The authors pointed out that the gentamicin V_d slightly varied across different ranges of age (39, 61 and 80 years old). Although age has been considered as an independent factor of nephrotoxicity and ototoxicity, several clinical studies mentioned that gentamicin clearance was influenced mainly by renal function and that the impact of age, by itself, is not significant [59-61].

4.1.4. Renal Therapy and other comorbidities

Among the articles included in this review, three gentamicin studies [22, 23, 27] and one amikacin study [17] included patients with continuous RRT (three under hemodialysis and one under EDD-f) in their respective PopPK model. Both amikacin CL under RRT were similar to each other with values of 4.69 L/h and 4.45 L/h for CVVH and for Continuous Venovenous Hemodiafiltration (CVVHDF), respectively [17]. In fact, it was hypothesized that the selection of a similar effluent rate in both RRT would result in a non-significant difference in amikacin PK between CVVH and

CVVHDF [62]. Teigen reported that gentamicin clearance during hemodialysis (4.69 L/h) was comparable to the clearance observed in patients with normal renal function [23]. Although CL_{CR} was deemed as a significant covariate in the evaluation of gentamicin clearance, it was demonstrated that residual renal function expressed as CL_{CR} is less accurate for hemodialysis patients compared to normal renal function patients or less advanced renal impairment [63]. Aminoglycosides usage in context of RRT has been widely studied in the literature [64-67]. The principal consensus of these studies was that dosing modifications such as increasing the dosing interval based on CL_{CR} or adjusting single-daily dosage are needed to be performed on impaired renal function patients. Furthermore, aminoglycosides serum levels must be monitored regularly to make the appropriate drug adjustments, especially considering aminoglycosides narrow therapeutic index.

As for other comorbidities, Gomes et al. developed their PopPK model based on endocarditis patients[29]. This particular infection is generally caused by pathogens such as staphylococci, streptococci and enterococci [68] and its complications such as sepsis or cardiovascular problems (congestive heart failure, acute pericarditis and myocarditis) can lead to an increased Vd [69]. Moreover, it was expressed that the augmented Vd would impact serum peak levels of gentamicin [29]. Therefore, it was suggested that endocarditis patients would need greater doses to increase probability of target attainment (PTA).

4.2. External validation and application

External validation is one of the strictest approaches in model testing and consists of applying a new dataset within a final model to determine the accuracy and reproducibility of the model and in which conditions it would be applicable. In this review, most studies performed at least advanced internal validation (n=13) but only three of them validated their model with another dataset [19, 29, 33] resulting with adequate bias and inaccuracy values. Although each of these models were externally validated using data from independent patients, this does not imply that these models could be easily applied into other datasets from similar populations. Moreover, while external validation is highly preferred during model evaluation, the amount of studies performing it is rather insufficient [70]. This lack of external validation could be due to the difficulty of collecting data from enough patients with similar characteristics from another ICU to build a high-

quality validation dataset. Furthermore, external validation in antimicrobials is known to often lead to inadequate bias and inaccuracy values [71-73], therefore suggesting that a certain challenge still remains.

4.3. Simulation of Dosing Regimens

Firstly, amikacin dosing recommendations in critically ill patients without RRT were simulated in two articles [16, 19]. In Boidin et al., an optimal initial amikacin dose of 3.5 g showed a better PTA for $C_{max} \geq 64$ mg/L and $AUC_{0-24} \geq 600$ mg*h/L compared to the conventional 30 mg/kg of corrected bodyweight (CBW), considering a MIC of 8 mg/L [16]. It was suggested that an increase of the dosing interval up to 36 or 48 hours might be feasible in critically ill patients with normal to moderate renal function. In fact, several recommendations were simulated based on different values of the two significant covariates in its respective PopPK model, CL_{CG} (10 mL/min to 250 mL/min) and BSA (1.5m² to 2.5m²). As for Aréchiga-Alvarado et al., different daily-dosing recommendations were simulated based on three different MIC (4 mg/L, 8 mg/L and 16 mg/L) and CL_{CR} ranging from 60 mL/min to 200 mL/min [19]. Considering a MIC of 8 mg/L, a 30 mg/kg daily dose would be able to show a TAR over 80% and 75% for patients with CL_{CR} lower than 140 mL/min and greater than 140 mL/min, respectively. As for amikacin dosing recommendations in critically ill patients RRT, two studies showed similar results in terms of optimal dosing regimens. In fact, Roger et al. and Carrié et al. suggested respectively that a dose of 25 mg/kg every 48 hours and a dose ranging from 25 mg/kg and 30 mg/kg every 36 to 48 hours were the most appropriate in order to maximize TAR for $C_{max}/MIC \geq 8$ and $AUC_{0-24} \geq 70$ or $AUC_{0-24} \geq 75$ with a MIC of 8 mg/L [17, 18].

Secondly, gentamicin and tobramycin dosing recommendations in critically ill patients without RRT were simulated in five different articles [24, 25, 32-34]. Three out of the five studies established similar dosing recommendations with initial starting dose of 6 to 7 mg/kg or a daily dose of 7 mg/kg [24-26]. The other study from Conil et al. provided a graphical representation of TAR for $C_{max} > 10$ mg/L, $C_{trough\ at\ 24h} < 1$ mg/L and AUC between 80 and 125 mg*h/L based on different fixed dose regimens [32]. Their main takeaway is that these targets were not reached simultaneously in more than 45% of patients. Furthermore, only half of the population was able to attain the target for AUC with daily fixed dosages of 375 and 400 mg. The other study from Aarons et al. simulated dosing regimens based on CL_{CR} values [33]. All dosing regimens proposed were

presented as a sequence: a fixed dose administered for the first 48h with a dosing interval ranging from 8h to 24h depending on the CL_{CR} . Following the first 48h, a maintenance dose was to be administered as per the same dosing interval. The first period of 48h was chosen upon the authors' assumption that aminoglycosides concentration was to be detectable, thus the possibility of dose adaptation [33]. As for patients under RRT, Teigen et al demonstrated that, based on PK/PD targets of $C_{max} \geq 8\text{mg/L}$ and AUC_{48} between 140 and 240 $\text{mg}\cdot\text{h/L}$, three fixed starting doses (300 mg, 240 mg, 220 mg) prior to dialysis is related to a better TAR compared to post dialysis administration [23]. Furthermore, Roberts et al. showed that a dosing of gentamicin 6 mg/kg every 48h and administered 30 minutes prior to RRT (EDD-f in this situation) was able to achieve PK/PD targets compared to daily 7 mg/kg administration[27].

5. Conclusion

Although many PopPK models for aminoglycosides exist in the literature, an important variability remains. Despite multiple covariates being tested across all studies, the significant covariates would still be creatinine clearance and bodyweight for aminoglycosides clearance and volume of distribution, respectively. Several limitations are to be considered: seven study populations had lower than 30 subjects and more than half of the articles had retrospective designs with few aminoglycosides' samples.

Although simulations have been carried out and help us to suggest optimal dosages, it should not be forgotten that many models have not been evaluated externally and therefore may not be generalizable. Moreover, these dosing regimens were taken from a small sample size of studies and additional research on simulated dosing regimens based on specific subpopulations should be necessary to optimize aminoglycosides individualized dosing. TDM remains essential in the ICU population to achieve therapeutic success while minimizing the likelihood of toxicity.

6. Conflict of interest

Alexandre Duong, Chantale Simard, David Williamson, Yi Le Wang and Amélie Marsot have no conflicts of interest that are directly relevant to the content of this article.

7. Funding

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Tables and Figures

Figure 1 : PRISMA Chart

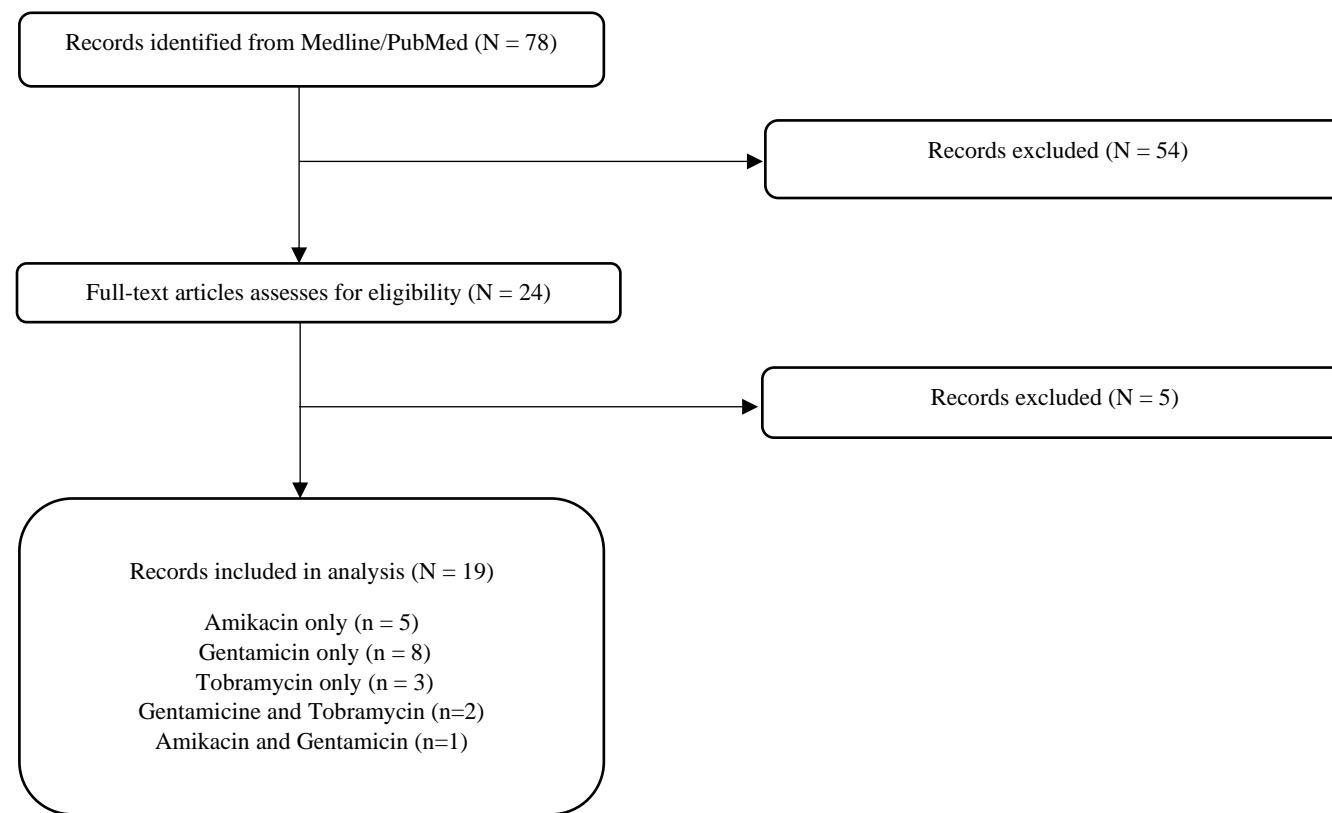
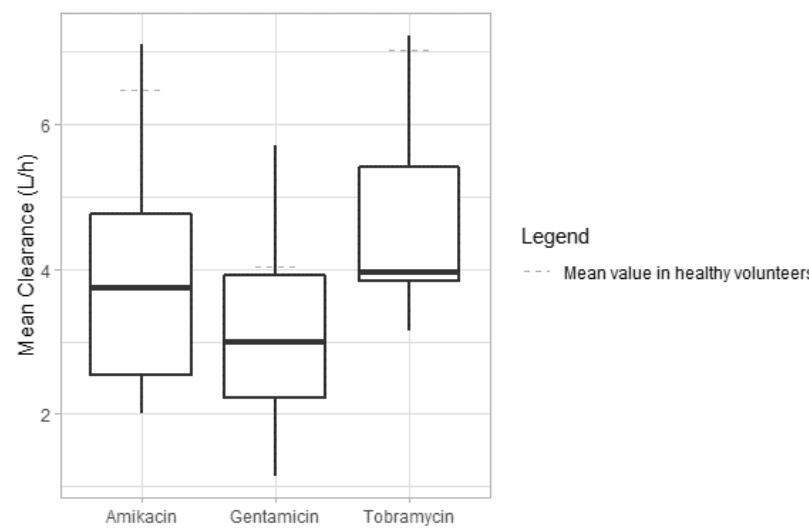


Figure 2

a) Range of mean clearance across studies stratified by aminoglycosides (Amikacin, Gentamicin and Tobramycin) with mean clearance value in healthy volunteers (dotted line).



b) Range of mean volume of distribution across studies stratified by aminoglycosides (Amikacin, Gentamicin and Tobramycin) with mean volume of distribution value in healthy volunteers (dotted line).

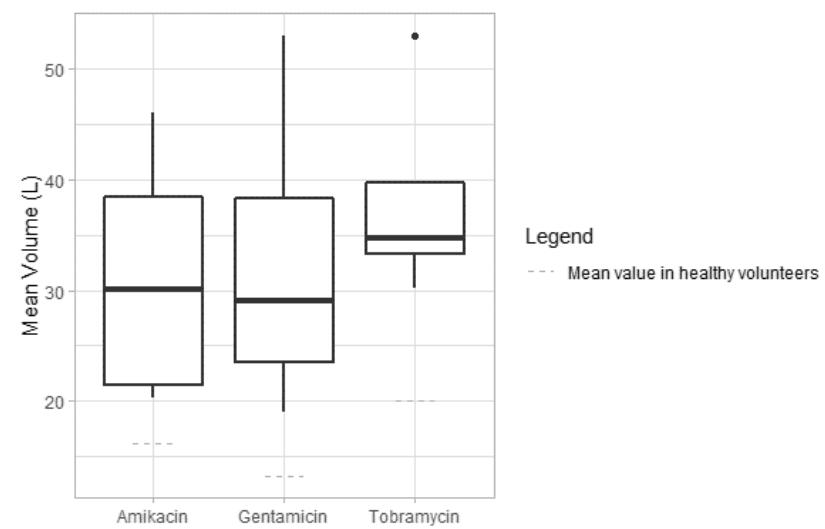
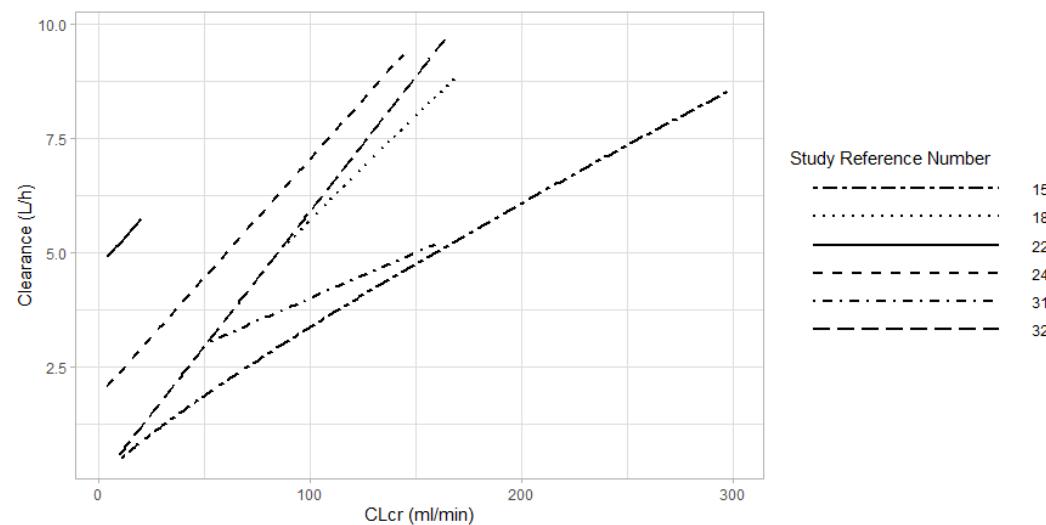
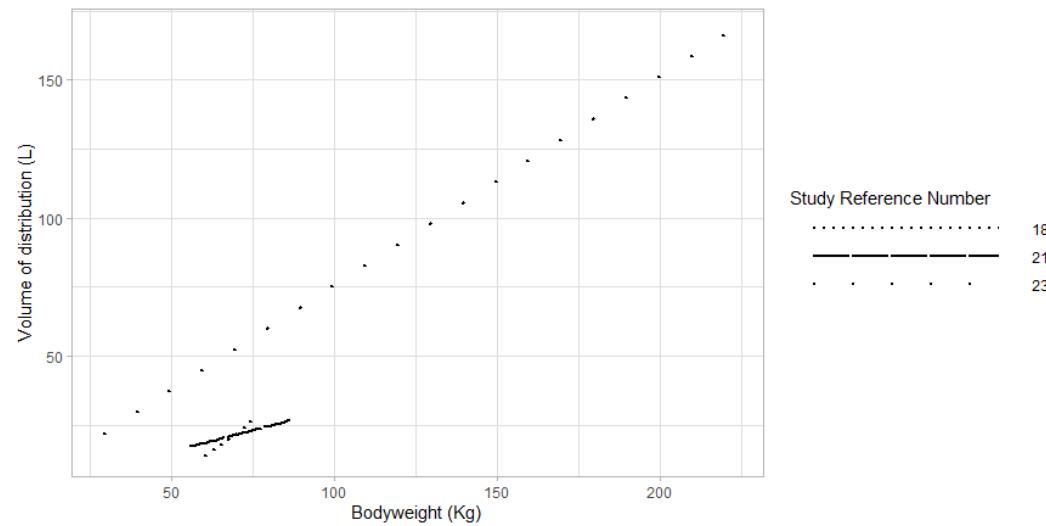


Figure 3

a) Aminoglycosides clearance values against range of creatinine clearance in their respective study.



b) Aminoglycosides volume of distribution values against range of bodyweight in their respective study.



Note: Two studies used IBW [19, 26] and one used TBW [24] in their model

Table 1 : Summary of patients' demographics and clinical protocol for all population-pharmacokinetic studies included in this review for Amikacin, Gentamicin and Tobramycin

Drug	Study	Year	Study type	Population					Aminoglycoside Administration		Samples			
				Patient Characteristics	N (Male/Female)	Age (years) a	Body Weight (kg) ^a	Height (cm) ^a	BMI (kg/m ²) ^a	Dosage regimen	Administered dose (mg/kg) ^a	Samples per patient	Total Samples	Sample frequency (hr)
Amikacin	Boidin C [16]	2019	Retrospective (TDM)	Critically ill with sepsis	166 (108/58)	65 (19-85)	76.5 (41.5-137.5)	170 (137-190)	25.6 (16-46)	Administered Daily	23.4 (11-39.7) [20.0-27.0] ^b	NR	395	Peak and trough
	Roger C [17]	2016	Observational Pharmacokinetic Study	Critically ill undergoing CVVH (n=9) and CVVHDF (n=11)	16 (12/4)	72 [65-75]	80 [73-89]	167 [162-178]	27 [24-32]	15-30 mg/kg every 24 or 36 h	NR	9	261	Predose, end of infusion (0.5), 1, 1.5, 2, 4, 8, 12 and 24
	Carrié C [18]	2020	Retrospective (TDM)	Critically ill septic patients treated by OA/NPT	70 (53/17)	65 [51-73]	80 [65-94]	NR	27 [25-32]	As per medical care by the local Department of Laboratory Medicine	26 [24-29] ^b	NR	179 (non-CRRT: 121, CRRT: 58)	Peak and trough
	Aréchiga-Alvarado NA [19]	2020	Prospective (TDM)	Critically ill mexican patients with suspected or proved infectious under treatment with amikacin	50 (45/5)	33.5 (18.0-64.0) ^b	70.0 (44.0-138.0)	170.1 ±7.9	24.0 (16.0-38.2) ^b	Once daily IV dosing	1000 (500-1000) mg ^c	2	80	0.5 and 12
	Petitcollin A [20]	2016	Prospective Pharmacokinetic Study	Ventilated critically ill patients on high-dose nebulized amikacin	20 (18/2)	57 (20-80)	67 (50-84)	NR	NR	20 mg/kg infusion of amikacin followed by either 3 other infusions or 3 nebulizations of 60 mg/kg amikacin (q24h)	NR	33 (11-45) ^b	522	0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24
	French MA [21]	1981	Prospective and retrospective (TDM)	Critically ill patients	25 (15/10)	58 ±14	NR	NR	NR	9 to 15 mg/kg per day ^d	40.60±42.67	NR	NR	NR

Table 1 Summary of patients' demographics and clinical protocol for all population-pharmacokinetic studies included in this review for Amikacin, Gentamicin and Tobramycin (continued)

Drug	Study	Year	Study type	Population					Aminoglycoside Administration		Samples			
				Patient Characteristics	N (Male/Female)	Age (years) a	Body Weight (kg) ^a	Height (cm) ^a	BMI (kg/m ²) ^a	Dosage regimen	Administered dose (mg/kg) ^a	Samples per patient	Total Samples	Sample frequency
Gentamicin	Hodiamont CJ [22]	2017	Retrospective (TDM)	Critically ill patients on or off CVVH	44 (20/24)	61 (20-78)	70.5 (42.0-116)	170 (154-195)	NR	Starting dose of 4 mg/kg TBW, except for patients treated for endocarditis due to Gram-Positive micro-organisms who were treated with 3 mg/kg in combination with a cell-wall-targeting antibiotic	4.0 (2.0-6.6) ^b	NR	303	0.5 and the second sample is collected the next morning at 06:00h, regardless of the time the first dose was administered
	Teigen MM [23]	2006	Prospective and retrospective (TDM)	Patients on hemodialysis receiving gentamicin to treat a suspected or proven infection	46 (23/23)	57.3 ± 17.3 (18-83)	72.4 ± 17.2 (42.1-100.5)	164.7 ± 11.6 (135-195)	NR	NR	NR	4.6 ± 2.2 (1-10)	NR	0.5, 1 sample at the beginning of dialysis, 1 sample at end of dialysis and 1 interdialytic blood sample taken prior to the next dialysis session
	Rea RS [24]	2008	Retrospective (TDM)	Critically ill patients	102 (45/57)	61.4 ± 16.8 (18.4 - 92.3)	81.4 ± 30.3 (29.0-222.3)	NR	NR	7 mg/kg/day	NR	2.1 (1-9)	211	NR
	Bos JC [25]	2019	Prospective observational pharmacokinetic study	Severally ill non-ICU Sub-Saharan African Adult patients	48 (24/24)	40 (20-86)	51 (33-76)	NR	NR	80 to 160 mg/kg q8h or 80 to 240 mg/kg q12 or 24h	NR	NR	141	Predose, 30 to 120 min after intravenous administration and two random time points during the dosing interval
	Hodiamont CJ [26]	2017	Prospective (TDM)	Critically ill patients	59 (30/29)	60.9 ± 17.2	79.2 ± 22.0	NR	NR	Fixed first dose of approximately 5 mg/kg. Patients who were treated for endocarditis with 3 mg/kg in combination with a beta-lactam antibiotic	5.1±1.1	6.7 ± 5.9	416	Peak and random timepoint between 6 and 23 hours after the administration
	Roberts JA [27]	2010	Prospective Pharmacokinetic Study	Critically ill patients with acute kidney injury necessitating extended daily diafiltration	14 (13/1)	66.0 (57.0-74.5) ^b	92.5 (80.0-111.1) ^b	NR	NR	NR	NR	NR	265	0, 0.25, 0.5, 1, 2, 3, 5, 8, 10
	Barletta JF [28]	2000	Prospective (TDM)	Critically ill trauma patients	19	40 ± 17 (17-75)	Adjusted (dosing) weight: 73.7 ± 15.9	NR	NR	NR	Gentamicine: 6.9 ± 0.39 (6-7.2) Tobramycine: 6.6 ± 1.03 (4.9-7.8)	NR	53	4 and 8
	Gomes A [29]	2017	Retrospective (TDM)	Endocarditis patients	65 (21/44)	69.3 (32-92)	76.2 (46-121)	173.9 (149-193)	NR	3 mg/kg q24h	NR	NR	221	NR
	Watling SM [30]	1993	Prospective (TDM)	Critically ill patients	36 (20/16)	54.7 ± 16.6	75.7 ± 16.4	172 ± 15	NR	3 mg/kg q12h, q18h, q24h, q36h or q72h	NR	2.8 ± 1.6	102	1 hour and at the dosing interval midpoint
	Kisor DF [31]	1992	Retrospective (TDM)	Patients with indicators of malnutrition (Bodyweight less than Ideal Bodyweight, low serum ALB)	17 (16/1)	73.8 ± 11.8	54.3 ± 9.9	NR	NR	NR	NR	8.0 ± 1.2	72	NR
	French MA [21]	1981	Prospective and retrospective (TDM)	Critically ill patients	25 (15/10)	62 ± 15	NR	NR	NR	3 to 5 mg/kg per day	31.73±27.26	NR	NR	NR

Table 1: Summary of patients' demographics and clinical protocol for all population-pharmacokinetic studies included in this review for Amikacin, Gentamicin and Tobramycin (continued)

Drug	Study	Year	Study type	Population				Aminoglycoside Administration		Samples				
				Patient Characteristics	N (Male/Female)	Age (years) ^a	Body Weight (kg) ^a	Height (cm) ^a	BMI (kg/m ²) ^a	Dosage regimen	Administered dose (mg/kg) ^a	Samples per patient	Total Samples	Sample frequency
Tobramycin	Conil JM [32]	2011	Retrospective (TDM)	Critically ill patients	32 (27/5)	62.5 ± 15.3	77.5 ± 18.8	NR	NR	5 mg/kg q24h for 3-5 days	NR	NR	NR	Peak and trough
	Aarons L [33]	1989	Retrospective (TDM)	Unselected population of patients treated with tobramycin	97 (52/45)	50.6 ± 19.0 (51.0;16-85) ^c	66.5 ± 12.5 (66.8; 42-120) ^c	NR	NR	NR	NR	(1-9)	322	2, 6 hr after the dose for patients with normal renal function 2,6, 12 and 24 hr for patients with impaired renal function
	Hennig S [34]	2013	Retrospective (TDM)	Patients with or without cystic fibrosis	208 (109/99)	31.7 (18.0-85.0)	58.0 (37.0-120.0)	NR	NR	NR	5.2 (0.9-12.0) per day	NR	CF: 4514 No CF: 1095	NR

ALB Albumin BMI Body Mass Index, CVVH Continuous Venovenous Hemofiltration, CVVHDF Continuous Venovenous Hemodiafiltration, ICU Intensive Care Unit, OA Open Abdomen, NPT Negative Pressure Therapy, NR Not Reported

^a Values are expressed as mean ± standard deviation (range) [interquartile range]^b Values are expressed as median (range)^c Values are expressed as mean ± standard deviation (median; range)

Table 2: Population pharmacokinetic modeling methods and techniques used by the studies included in the review

Drug	Study	Modeling			Simulation	
		Software	Model	Evaluation	Optimal Dosing Regimen	Target
Amikacin	Boidin C [16]	NPAG (Pmetrics)	2-compartment	Advanced internal	Optimal initial amikacin dose for C_{max} : 3.5 g Optimal initial amikacin dose for AUC_{0-24} : 3.8 g Optimal doses were based on a MIC of 8 mg/L	$C_{max}/MIC \geq 8$, $AUC_{0-24}/MIC \geq 75$ and $C_{min} \leq 2.5 \text{ mg/L}$
	Roger C [17]	NPAG (Pmetrics)	2-compartment	Advanced internal (bootstrap, n= 1000)	25 mg/kg every 48 h in critically ill patients receiving CRRT based on a MIC of 8 mg/L	$C_{max}/MIC \geq 8$ and $C_{min} \leq 2.5 \text{ mg/L}$
	Carrié C [18]	Monolix	2-compartment	Advanced internal (NPDE)	25-30 mg/kg every 36-48 h based on a MIC of 8 mg/L	$C_{max}/MIC \geq 8$, $AUC_{0-24}/MIC \geq 75$ and $C_{min} \leq 2.5 \text{ mg/L}$
	Aréchiga-Alvarado NA [19]	NONMEM 7.3	1-compartment	Advanced internal (bootstrap, n=1000) and external (13 patients)	Based on a MIC of 8 mg/L and a dose of 30 mg/kg, the probability of having $C_{max}/MIC \geq 8$ was above 75% for creatinine clearance ranging from 60 ml/min to 200 ml/min ^a	$C_{max}/MIC \geq 8$ and $AUC_{0-24}/MIC \geq 75$
	Petitcollin A [20]	Monolix 4.2.3	2-compartment	Advanced internal (NPDE)	—	—
	French MA [21]	NONLIN	2-compartment	NR	—	—

Table 2: Population pharmacokinetic modeling methods and techniques used by the studies included in the review (continued)

Drug	Study	Modeling			Simulation	
		Software	Model	Evaluation	Optimal Dosing Regimen	Target
Gentamicin	Hodiamont CJ [22]	NONMEM 7.1.2	2-compartment	Advanced internal (bootstrap, n= 1000)	—	
	Teigen MM [23]	NONMEM 5	1-compartment	Basic internal	Predialysis administration of 300 mg, 240 mg and 220 mg as first, second and third dose, respectively for patients who dialize 3 times a week	$C_{max} \geq 8\text{mg/L}$ $AUC_{min,48h} \geq 140$ $AUC_{max,48h} \leq 240$
	Rea RS [24]	NONMEM 5.1	1-compartment	Advanced internal (bootstrap, n= 1000)	Initial doses of 7 mg/kg of either gentamicin or tobramycin. Then, it is recommended to verify Cmax after the first dose and determining MIC for the pathogen(s) with adjustment of subsequent doses to achieve the PD target ^b	$C_{max}/MIC \geq 10$
	Bos JC [25]	NONMEM 7.1.2	1-compartment	Advanced internal (bootstrap, n= 1000)	7 mg/kg/day considering a MIC of 2 mg/L	$C_{max}/MIC \geq 8$
	Hodiamont CJ [26]	NONMEM 7.2	2-compartment	Advanced internal (bootstrap, n= 1000)	6 mg/kg as starting dose	C_{max} therapeutic range of 15-20 mg/L
	Roberts JA [27]	NONMEM 6.1	2-compartment	Advanced internal (bootstrap, n= 1000)	6 mg/kg every 48h before the commencement of EDD-f	$C_{max} > 10 \text{ mg/L}$ and $70 \text{ mg}\cdot\text{h/L} \leq AUC_{0-24} \leq 120 \text{ mg}\cdot\text{h/L}$
	Barletta JF [28]	Nonlinear mixed effect modelling	1-compartment	NR	—	—
	Gomes A [29]	MwPharm	1-compartment	Advanced internal (bootstrap, n=1000) and external (14 patients)	—	—
	Watling SM [30]	NPEM ^c	1-compartment	External of dosing nomogram only (15 patients)	—	—
	Kisor DF [31]	NPEM	1-compartment	NR	—	—
	French MA [21]	NONLIN	2-compartment	NR	—	—

Table 2: Population pharmacokinetic modeling methods and techniques used by the studies included in the review

Drug	Study	Modeling			Simulation	
		Software	Model	Evaluation	Optimal Dosing Regimen	Target
Tobramycin	Conil JM [32]	NONMEM 5	2-compartment	Advanced Internal (NPDE and bootstrap, n=1000) and External (17 patients)	Peak and AUC pharmacodynamic targets could not be reached simultaneously in more than 45% of the ICU patient population. Combination therapy in addition to TDM are required to manage efficacy and toxicity	$C_{max}/MIC > 10$, $C_{min} \leq 1$ mg/L AUC between 80 and 125 mg·h/L for $MIC \leq 1$ mg/L
	Aarons L [33]	NONMEM	2-compartment	External (34 patients)	First 48 hr: 100mg Q8h and Maintenance dose : 120 mg Q8h, patient with $CL_{cr} > 100$ ml/min First 48 hr: 80mg Q8h and Maintenance dose : 90 mg Q8h, patient with $CL_{cr} = 75$ ml/min First 48 hr: 93mg Q12h and Maintenance dose : 90 mg Q12h, patient with $CL_{cr} = 50$ ml/min First 48 hr: 60mg Q12 and Maintenance dose : 54mg Q12h, patient with $CL_{cr} = 30$ ml/min First 48 hr: 80mg Q24 and Maintenance dose : 70mg Q24h, patient with $CL_{cr} = 20$ ml/min First 48 hr: 67mg Q24 and Maintenance dose : 54mg Q24h, patient with $CL_{cr} = 15$ ml/min First 48 hr: 60mg Q24 and Maintenance dose : 35mg Q24h, patient with $CL_{cr} = 10$ ml/min	$C_{max} = 6$ mg/L and average concentrations within a dosing interval ≤ 4 mg/L
	Hennig S [34]	NONMEM 7.2	2-compartment	Advanced Internal (bootstrap, n=300)	11 mg/kg/day for Cystic Fibrosis patients	$C_{max} = 20$ mg/L (relating to a 1-h peak/MIC ratios of 20/2) and $C_{min} < 1$ mg/L

AUC area under the concentration-time curve, *CL_{cr}* creatinine clearance, *C_{max}* maximum concentration, *C_{min}* minimum concentration, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit, *MIC* minimal inhibitory concentration, *NPDE* Normalized prediction distribution error, *NR* Not Reported

^a Graphical representation of probability of target attainment based on different amikacin dosing regimens (15 mg/kg to 70 mg/kg), different MIC (4 mg/L to 16 mg/L) and different values of creatinine clearance

^b Table probability of $C_{max} \geq 10 \times MIC$ by different MIC and aminoglycoside dose

^c PK parameters were calculated using Sawchuk-Zaske method

Table 3: Covariates that were included or evaluated for inclusion by the population pharmacokinetic models included in this review

Drug	Study	Tested and significant covariates																													
		Age	Sex	Height	Race	AdjBW ^a	AdjBW ^b	AdjBW ^c	TBW	IBW	BW _{AD-40}	LBW	LBMc	FFM	BSA	BMI	Scr	hemoglobin	Salb	CL _{CG}	CL _{hf}	CL _{hd}	CL _{CKD-EPI}	CL _{MDRD}	CalcCLCR	CL _{Robert}	ARC	FCR	GFR	GFR _{MDRD}	GFR _{CKD-EPI}
Amikacin	Boidin C [16]	○	○	○		○	○	○	○	○				●	○	○			●									○	○		
	Roger C [17]	○						● ^d		○						○		○		●	●										
	Carrié C [18]	○	○			●			○											●											
	Aréchiga-Alvarado NA [19]	○	○			○			○	●							○	○		○	●			○	○						
	Petitcollin A [20]	○	○						○									○			●										
	French MA ⁱ [21]																														
Gentamicin	Hodiamont CJ [22]	○	○	○				●									○		○	○				○							
	Teigen MM [23]								○	○									● ^f												
	Rea RS [24]	○	○		○			●									○														
	Bos JC [25]	○	○	○					○								○	○	○	○	●			○							
	Hodiamont CJ [26]							○	○	○																					
	Roberts JA [27]	○						● ^g		● ^h									○												
	Barletta JF [28]	○																	○												
	Gomes A [29]	○	○	○				●			○						○	○													
	Watling SM [30]																														
	Kisor DF ⁱ [31]																														
Tobramycin	Conil JM [32]		●						○								○	○					○								
	Aarons L [33]	●	○	○					○										●												
	Hennig S [34]	●	○	○					○									○													

ADJ Adjusted body weight, ALAT Alanine amino transferase, APACHE II Acute Physiology and chronic health evaluation II, ARC Augmented renal clearance (ARC) defined as a CLCR ≥ 130 mL/min, ASAT Aspartate amino transferase, BMI Body Mass Index, BSA Body Surface Area, BUN Blood Urea Nitrogen, BW_{AD-40} Difference in patient's weight between the time of admission and the sampling day, CalcCLCR Creatinine clearance calculated from the creatinine concentration in a 6-h urine portion, CBW Corrected body weight, CF Cystic Fibrosis, CLCKD-EPI Creatinine clearance estimated with CKD-EPI, CLCG Creatinine Clearance estimated by Cockcroft-Gault equation, CL_{hf} total amikacin clearance on hemodialfiltration, CL_{hd} total amikacin clearance on hemofiltration, CL_{MDRD} Creatinine clearance calculated with MDRD, CL_{Robert} Creatinine Clearance estimated by Robert equation, CVVH Continuous venovenous haemofiltration, EDD-f Extended daily dialfiltration, FCR Inverse of the final plasma creatine concentration recorded in μmol/L before commencement of EDD-f, FFM Fat free mass, Fluid_{NPT} Amount of fluids collected by the NPT over the sampling day, GFR Glomerular filtration rate, GFR_{MDRD} GFR estimated by the equation from the Modification of Diet in Renal Disease, GFR_{CKD-EPI} GFR estimated by the equation from the Chronic Kidney Disease, IBW Ideal body weight, ICU Intensive Care Unit, LBW Lean body weight, LBMc Lean body mass according to the equation of Chennavasin (source), NPT Negative Pressure Therapy, NSAIDs Nonsteroidal anti-inflammatory drugs, Salb Serum albumin, SAPSII Simplified acute physiology score II, SCR Serum Creatinine, SOFA Sepsis-related organ failure assessment score

● Tested and significant

○ Tested and not significant

^a Adjusted body weight (ABW) was determined as follows : i) for $BMI \leq 30 \text{ kg/m}^2$, ABW = TBW; ii) for $BMI > 30 \text{ kg/m}^2$, ABW = ideal body weight (IBW) + 0.43 (TBW - IBW), with IBW calculated according to the Lorenz formula [74]

^b Adjusted body weight was calculated as proposed by Bauer et al.: AdjBW = 0.4(TBW-IBW) + IBW for morbidly obese patients (IBW/TBW ratio of ≥ 1.9)

^c Adjusted body weight proposed by Traynor et al. Was adapted according to French recommendations with a weight correction factor for overweight patients (IBW/TBW ratio of ≥ 1.25) and calculated as CBW = 0.43 (TBW-IBW)+IBW

^d Described as Actual body weight

^e Modified SOFA score (without neurologic and renal components)

^f Creatinine Clearance estimated with Cockcroft-Gault with ideal body weight

^g Normalized to 70 kg

^h Normalized to 55 kg

ⁱ Covariate models were not used in this study

Table 3: Covariates that were included or evaluated for inclusion by the population pharmacokinetic models included in this review (continued)

Drug	Study	Tested and significant covariates																	
		SOFA score	SAPSII score	APACHE II score	ALAT	ASAT	Urea	BUN	Total proteins	Total bilirubin	Total daily diuresis	Serum electrolytes (sodium, potassium, chloride, calcium, phosphorus and magnesium)	24 hr fluid balance	Fluid balance since ICU admittance	Administration of total parenteral nutrition	Flow rate of ultrafiltrate during CVVH	Residual Renal function	Filter age	Fluid _{NPT}
Amikacin	Boidin C [16]	○	○	○	○												○	○	
	Roger C [17]																		
	Carrié C [18]	○ ^e										○							○
	Aréchiga-Alvarado NA [19]		○			○	○	○	○	○									
	Petitcollin A [20]																		
	French MA ⁱ [21]																		
Gentamicin	Hodiamont CJ [22]		○									○		○	○	○	○		●
	Teigen MM [23]																		
	Rea RS [24]																		
	Bos JC [25]																		
	Hodiamont CJ [26]																		
	Roberts JA [27]																		
	Barletta JF [28]																		
	Gomes A [29]																		
	Watling SM [30]																		
	Kisor DF ⁱ [31]																		
Tobramycin	Conil JM [32]		○																
	Aarons L [33]																		
	Hennig S [34]																		

ADJ Adjusted body weight, ALAT Alanine amino transferase, APACHE II Acute Physiology and chronic health evaluation II, ARC Augmented renal clearance (ARC) defined as a CLCR ≥ 130 mL/min, ASAT Aspartate amino transferase, BMI Body Mass Index, BSA Body Surface Area, BUN Blood Urea Nitrogen, BW_{AD-0} Difference in patient's weight between the time of admission and the sampling day, CalcCLCR Creatinine clearance calculated from the creatinine concentration in a 6-h urine portion, CBW Corrected body weight, CF Cystic Fibrosis, CLCKD-EPI Creatinine clearance estimated by CKD-EPI, CLCG Creatinine Clearance estimated by Cockcroft-Gault equation, CL_{hf} total amikacin clearance on hemodiafiltration, CL_{hf} total amikacin clearance on hemofiltration, CL_{MDRD} Creatinine clearance calculated with MDRD, CL_{Robert} Creatinine Clearance estimated by Robert equation, CVVH Continuous venous haemofiltration, EDD-f Extended daily diafiltration, FCR Inverse of the final plasma creatinine concentration recorded in $\mu\text{mol/L}$ before commencement of EDD-f, FFM Fat free mass, Fluid_{NPT} Amount of fluids collected by the NPT over the sampling day, GFR Glomerular filtration rate, GFR_{MDRD} GFR estimated by the equation from the Modification of Diet in Renal Disease, GFR_{CKD-EPI} GFR estimated by the equation from the Chronic Kidney Disease, IBW Ideal body weight, ICU Intensive Care Unit, LBW Lean body weight, LBMc Lean body mass according to the equation of Chennavasin (source), NPT Negative Pressure Therapy, NSAIDs Nonsteroidal anti-inflammatory drugs, SAlb Serum albumin, SAPSII Simplified acute physiology score II, SCR Serum Creatinine, SOFA Sepsis-related organ failure assessment score

● Tested and significant

○ Tested and not significant

^a Adjusted body weight (ABW) was determined as follows : i) for $\text{BMI} \leq 30 \text{ kg/m}^2$, ABW = TBW; ii) for $\text{BMI} > 30 \text{ kg/m}^2$, ABW = ideal body weight (IBW) + 0.43 (TBW - IBW), with IBW calculated according to the Lorenz formula [74]

^b Adjusted body weight was calculated as proposed by Bauer et al.: AdjBW = 0.4(TBW-IBW) + IBW for morbidly obese patients (IBW/TBW ratio of ≥ 1.9)

^c Adjusted body weight proposed by Traynor et al. Was adapted according to French recommendations with a weight correction factor for overweight patients (IBW/TBW ratio of ≥ 1.25) and calculated as CBW = 0.43 (TBW-IBW)+IBW

^d Described as Actual body weight

^e Modified SOFA score (without neurologic and renal components)

^f Creatinine Clearance estimated with Cockcroft-Gault with ideal body weight

^g Normalized to 70 kg

^h Normalized to 55 kg

ⁱ Covariate models were not used in this study

Table 3: Covariates that were included or evaluated for inclusion by the population pharmacokinetic models included in this review (continued)

Drug	Study	Tested and significant covariates								Usage of concomitant medication							
		Childhood (<18 years)	Study Site	Reason for admission	Usage of CVVH	Usage of mechanical ventilation	Disease presence (CF or no-CF)	Diagnosis of diabetes mellitus and/or arterial hypertension	Gas humidification	Vasopressin	Aminoside used	NSAIDs	Opiod analgesics	Cephalosporins	Diuretics	Antimycotics	Inotropics agents
Amikacin	Boidin C [16]									○							
	Roger C [17]									○							
	Carrié C [18]											○	○	○	○	○	○
	Aréchiga-Alvarado NA [19]					○		○	○								
	Petitcollin A [20]																
	French MA ⁱ [21]																
Gentamicin	Hodiamont CJ [22]	●															
	Teigen MM [23]																
	Rea RS [24]																
	Bos JC [25]																
	Hodiamont CJ [26]																
	Roberts JA [27]																
	Barletta JF [28]																
	Gomes A [29]																
	Watling SM [30]																
	Kisor DF ⁱ [31]																
Tobramycin	Conil JM [32]	○	○	○													
	Aarons L [33]																
	Hennig S [34]					○											

ADJ Adjusted body weight, ALAT Alanine amino transferase, APACHE II Acute Physiology and chronic health evaluation II, ARC Augmented renal clearance (ARC) defined as a CLCR \geq 130 mL/min, ASAT Aspartate amino transferase, BMI Body Mass Index, BSA Body Surface Area, BUN Blood Urea Nitrogen, BW_{AD-i} Difference in patient's weight between the time of admission and the sampling day, CalcCLCR Creatinine clearance calculated from the creatinine concentration in a 6-h urine portion, CBW Corrected body weight, CF Cystic Fibrosis, CLCKD-EPI Creatinine clearance estimated with CKD-EPI, CLCG Creatinine Clearance estimated by Cockcroft-Gault equation, CL_{hd} total amikacin clearance on hemodialfiltration, CL_{hf} total amikacin clearance on hemofiltration, CL_{MDRD} Creatinine clearance calculated with MDRD, CL_{Robert} Creatinine Clearance estimated by Robert equation, CVVH Continuous venovenous haemofiltration, EDD-f Extended daily diafiltration, FCR Inverse of the final plasma creatine concentration recorded in $\mu\text{mol/L}$ before commencement of EDD-f, FFM Fat free mass, Fluid_{NPT} Amount of fluids collected by the NPT over the sampling day, GFR Glomerular filtration rate, GFR_{MDRD} GFR estimated by the equation from the Modification of Diet in Renal Disease, GFR_{CKD-EPI} GFR estimated by the equation from the Chronic Kidney Disease, IBW Ideal body weight, ICU Intensive Care Unit, LBW Lean body weight, LBMc Lean body mass according to the equation of Chennavasin (source), NPT Negative Pressure Therapy, NSAIDs Nonsteroidal anti-inflammatory drugs, SA1b Serum albumin, SAPSII Simplified acute physiology score II, SCR Serum Creatinine, SOFA Sepsis-related organ failure assessment score

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^a Adjusted body weight (ABW) was determined as follows : i) for $\text{BMI} \leq 30 \text{ kg/m}^2$, ABW = TBW; ii) for $\text{BMI} > 30 \text{ kg/m}^2$, ABW = ideal body weight (IBW) + 0.43 (TBW - IBW), with IBW calculated according to the Lorenz formula [74]

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^d Described as Actual body weight

^e Modified SOFA score (without neurologic and renal components)

^f Creatinine Clearance estimated with Cockcroft-Gault with ideal body weight

^g Normalized to 70 kg

^h Normalized to 55 kg

ⁱ Covariate models were not used in this study

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