Aminoglycosides in the Intensive Care Unit: What Is New in Population PK Modeling?

Alexandre Duong 1,2,*, Chantale Simard 3,4, Yi Le Wang 1,2, David Williamson 1,5 and Amélie Marsot 1,2,6

1 Faculté de Pharmacie, Université de Montréal, Montréal, QC H3T 1J4, Canada; yi.le.wang@umontreal.ca (Y.L.W.); david.williamson@umontreal.ca (D.W.);
amelie.marsot@umontreal.ca (A.M.)
2 Laboratoire de Suivi Thérapeutique Pharmacologique et Pharmacocinétique, Faculté de Pharmacie, Université de Montréal, Montréal, QC H3T 1J4, Canada
3 Faculté de Pharmacie, Université Laval, Québec, QC G1V 0A6, Canada; chantale.simard@pha.ulaval.ca
4 Centre de Recherche, Institut Universitaire de Cardiologie et Pneumologie de Québec, Québec, QC G1V 4G5, Canada
5 Hôpital Sacré-Cœur de Montréal, Montréal, QC H4J 1C5, Canada
6 Centre de Recherche, CHU Sainte Justine, Montréal, QC H3T 1C5, Canada
* Correspondence: Alexandre.duong.1@umontreal.ca; Tel.: +1-514-343-6111

Abstract: Background: Although aminoglycosides are often used as treatment for Gram-negative infections, optimal dosing regimens remain unclear, especially in ICU patients. This is due to a large between- and within-subject variability in the aminoglycoside pharmacokinetics in this population. Objective: This review provides comprehensive data on the pharmacokinetics of aminoglycosides in patients hospitalized in the 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. Method: A literature search was conducted in 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, 11, and five models, respectively. A two-compartment model was used to describe amikacin and tobramycin pharmacokinetics, whereas a 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. Conclusions: This review showed models developed for amikacin, from 2015 until now, and for gentamicin and tobramycin from the past decades. Despite the 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 aminoglycoside pharmacokinetics in ICU patients.

Keywords: aminoglycosides; population pharmacokinetic modeling; intensive care unit; critically ill 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 an 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 ($C_{\text{max}}$) over minimum inhibitory concentration (MIC) ratio greater than 10 is warranted for a clinical response [6]. Although the $C_{\text{max}}$/MIC target is primarily used in clinical situations due to its simplicity, multiple studies have shown that an 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 the narrow therapeutic index of aminoglycosides with potential nephrotoxicity and oto-toxicity, 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 aminoglycoside clinical response based on ICU patients’ characteristics. These studies have used nonlinear mixed effects modeling to target and quantify the contribution of specific demographic and pathophysiological characteristics that may influence the aminoglycoside PK profile. This modeling 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 was 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 in 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 OR severe OR acute OR serious) 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 intravenous amikacin, gentamicin, or tobramycin; (3) the studied population consisted of ICU adult patients; (4) the article was published in the English language.
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 intravenous amikacin, gentamicin, or tobramycin; (3) the studied population consisted of ICU adult patients; (4) the article was published in the English language.

2.3. Exclusion Criteria
We excluded articles from this review if they met one of the following criteria: (1) a noncompartmental 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]; (4) they were review articles.

2.4. Data Extraction
The following information was 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, and 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 (Supplementary Materials).

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, six, 11, and five 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. The mean population age from these studies ranged from 32 years [34] to 74 years [31] with the 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 numbers of retrospective and prospective designs were similar, with 10 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]. Furthermore, seven studies included fewer 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 the 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 3 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 included 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), while 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 [21,22,26,27]).
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 Type | Year | Study Type                  | Population Characteristics | Aminoglycoside Administration | Samples |
|---------------|------------|------|-----------------------------|-----------------------------|-----------------------------|---------|
| Amikacin      | Retrospective (TDM) | 2019 | Critically ill with sepsis  | 166 (Male/Female) 65 (19-81) | 23.4 (11-39.7) | NR 395 |
|               | Retrospective (TDM) | 2016 | Observational pharmacokinetic study | Critically ill undergoing CVVH (n = 10) | 16 (32-4) | 15-30 mg/kg, every 24 or 36 h | NR 9 |
|               | Retrospective (TDM) | 2020 | Critically ill septic patients treated by OA/NPT | 70 (53/17) | 27 (25-32) | As per medical care by the local Department of Laboratory Medicine | NR 179 |
| Gentamicin    | Prospective (TDM) | 2017 | Critically ill patients on off CVVH | 44 (20-26) | 4.0 ± 0.6 | NR 303 |
|               | Prospective and retrospective (TDM) | 2006 | Patients on hemodialysis receiving gentamicin to treat a suspected or proven infection | 46 (23-23) | 4.8 ± 2 (1-10) | NR 211 |
|               | Prospective (TDM) | 2019 | Severely ill non-ICU sub-Saharan Adult patients | 48 (24-24) | 5.1 ± 1.1 | NR 416 |
|               | Prospective (TDM) | 2017 | Critically ill patients with acute kidney injury necessitating extended daily dialysis | 59 (30-29) | 5.1 ± 1.1 | Peak and random timepoint between 6 and 23 h after the administration |
|               | Prospective (TDM) | 2010 | Critically ill patients with acute kidney injury necessitating extended daily dialysis | 14 (13/1) | 0.025, 0.5, 1, 2, 3, 4, 8, and 10 | NR 266 |
### Table 1. Cont.

| Drug          | Study                                      | Year | Study Type (TDM) | Population Description                                      | N (Male/Female) | Age (Years) ± (range) | Body Weight (kg) ± (range) | Height (cm) ± (range) | BMI (kg/m²) ± (range) | Dosage Regimen | Administered Dose (mg/kg) ± (range) | Samples per Patient | Total Samples | Sample Frequency (h) |
|---------------|--------------------------------------------|------|-----------------|------------------------------------------------------------|-----------------|------------------------|--------------------------|------------------------|------------------|-----------------|--------------------------|--------------------|--------------|-----------------------|
| Gentamicine   | Barletta JF [28]                          | 2000 | Prospective     | Critically ill trauma patients                              | 19 (17–75)      | 40 ± 17                | 73.7 ± 15.9              | NR                     | NR               | NR             | Gentamicine: 6.9 ± 0.9 (6-7.2) Tobramycin: 6.6 ± 1.0 (4.9-7.3) | NR                  | 53           | 4 and 8               |
| Tobramycin    | Gomes A [29]                              | 2017 | Retrospective   | Endocarditis patients                                       | 65 (21/44)      | 69.3 ± 12.6 (32–92)    | 76.2 ± 12.1 (46–121)     | 173 ± 19.3 (149–193)    | NR               | NR             | 5 mg/kg q24 h             | NR                  | NR           | 221                   |
|              | Watling SM [30]                           | 1993 | Prospective     | Critically ill patients                                     | 36 (20/16)      | 54.7 ± 14.6 (16–66)    | 79.7 ± 16.4 (179–210)    | 172 ± 15 (160–200)      | NR               | NR             | 3 mg/kg q24 h, 6 h, q48 h 5 mg/kg q24 h, q48 h, q72 h | NR                  | 2.8 ± 1.4    | 102                   |
|              | Kaiser DF [31]                            | 1992 | Retrospective   | Patients with indicators of malnutrition (bodyweight less than ideal bodyweight, low serum ALB) | 17 (16/1)       | 72.8 ± 11.8 (66-100)   | 54.3 ± 9.9 (44–72)       | NR                     | NR               | NR             | 3 mg/kg q24 h, 6 h, q48 h 5 mg/kg q24 h, q48 h, q72 h | NR                  | 4.0 ± 1.2    | 72                    |
|              | French MA [32]                            | 1981 | Prospective and retrospective | Critically ill patients                                          | 25 (15/10)      | 62 ± 15 (51–85)        | NR                       | NR                     | NR               | NR             | 3 to 5 mg/kg per day                  | NR                  | 31.7 ± 27.6  | NR                    |
|              | Conil JM [33]                             | 2011 | Retrospective   | Critically ill patients                                     | 32 (27/5)       | 62.5 ± 15.3 (33–190)   | 77.5 ± 18.6 (50–215)     | NR                     | NR               | NR             | 5 mg/kg q24 h for 3–5 days             | NR                  | NR           | NR                    |
|              | Hennig S [34]                             | 2013 | Retrospective   | Patients with or without cystic fibrosis                    | 208 (109/99)    | 31.7 ± 18.0 (18–68)    | 56.0 ± 12.0 (27–80)      | NR                     | NR               | NR             | 5.2 ± 1.0 (1–12) per day               | NR                  | NR           | CF: 4914 No CF: 1099 | 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. * Values are expressed as the mean ± standard deviation (range) [interquartile range]. † Values are expressed as the median (range) [interquartile range]. ‡ Values are expressed as the mean ± standard deviation (median; range).
Table 2. Population pharmacokinetic modeling methods and techniques used by the studies included in the review.

| Drug      | Study                        | Software/Model | Optimization | Software/Model | Evaluation | Optimal Dosing Regimen | Target |
|-----------|------------------------------|----------------|--------------|----------------|------------|-------------------------|--------|
| Amikacin  | Boidin C [16]               | NPAG (Pmetrics) | 2 compartments | Advanced internal | Optimal initial amikacin dose for $C_{\text{max}}$: 3.5 g | $C_{\text{max}}$/MIC ≥ 8, AUC$_{0–24}$/MIC ≥ 75 and $C_{\text{min}}$ ≤ 2.5 mg/L |
|           |                              |                |              |                |            |                         |        |
|           | Roger C [17]                 | NPAG (Pmetrics) | 2 compartments | Advanced internal (bootstrap, n = 1000) | 25 mg/kg every 48h in critically ill patients receiving CRRT based on an MIC of 8 mg/L | $C_{\text{max}}$/MIC ≥ 8 and $C_{\text{min}}$ ≤ 2.5 mg/L |
|           | Carrié C [18]                | Monolix         | 2 compartments | Advanced internal (NPDE) | 25–30 mg/kg every 36–48h based on an MIC of 8 mg/L | $C_{\text{max}}$/MIC ≥ 8, AUC$_{0–24}$/MIC ≥ 75 and $C_{\text{min}}$ ≤ 2.5 mg/L |
|           | Anéchiga-Alcarado NA [19]    | NONMEM 7.3      | 1 compartment | Advanced internal (bootstrap, n = 1000) and external (13 patients) | Based on an MIC of 8 mg/L and a dose of 30 mg/kg, the probability of having $C_{\text{max}}$/MIC ≥ 8 was above 75% for creatinine clearance ranging from 60 mL/min to 200 mL/min$^a$ | $C_{\text{max}}$/MIC ≥ 8 and AUC$_{0–24}$/MIC ≥ 75 |
|           | Petitcollin A [20]           | Monolix 4.2.3   | 2 compartments | Advanced internal (NPDE) | –            | –                       | –      |
|           | French MA [21]               | NONLIN          | 2 compartments | NR             | –            | –                       | –      |
|           | Hodiamont CJ [22]            | NONMEM 7.1.2    | 2 compartments | 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 dialyze 3 times a week | $C_{\text{max}}$ ≥ 8 mg/L, AUC$_{\text{min},48h}$ ≥ 140, AUC$_{\text{max},48h}$ ≤ 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 $C_{\text{max}}$ after the first dose and determining MIC for the pathogen(s) with adjustment of subsequent doses to achieve the PD target$^b$ | $C_{\text{max}}$/MIC ≥ 10 |
|           | Bos JC [25]                  | NONMEM 7.1.2    | 1 compartment | Advanced internal (bootstrap, n = 1000) | 7 mg/kg/day considering an MIC of 2 mg/L | $C_{\text{max}}$/MIC ≥ 8 |
|           | Hodiamont CJ [26]            | NONMEM 7.2      | 2 compartments | Advanced internal (bootstrap, n = 1000) | 6 mg/kg as starting dose | $C_{\text{max}}$ therapeutic range of 15–25 mg/L |
|           | Roberts JA [27]              | NONMEM 6.1      | 2 compartments | Advanced internal (bootstrap, n = 1000) | 6 mg/kg every 48h before the commencement of EDD-f | $C_{\text{max}}$ > 10 mg/L and 70 mg h/L ≤ AUC$_{0–24}$ ≤ 120 mg 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 compartments | NR             | –            | –                       | –      |
Table 2. Cont.

| Drug    | Study          | Software | Model       | Evaluation                                                                 | Optimal Dosing Regimen                                                                 | Target                                                                 |
|---------|----------------|----------|-------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Tobramycin | Conil JM [32]  | NONMEM 5 | 2 compartments | 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. | \( C_{\text{max}} / \text{MIC} > 10, C_{\text{min}} \leq 1 \text{ mg/L} \)  
AUC between 80 and 125 mg h/L for MIC \( \leq 1 \text{ mg/L} \) |
|         | Aarons L [33]  | NONMEM   | 2 compartments | External (34 patients) |                                                                                          | First 48 h: 100 mg Q8 h and Maintenance dose: 120 mg Q8 h, patient with CLcr > 100 mL/min  
First 48 h: 80 mg Q8 h and Maintenance dose: 90 mg Q8 h, patient with CLcr = 75 mL/min  
First 48 h: 93 mg Q12 h and Maintenance dose: 90 mg Q12 h, patient with CLcr = 50 mL/min  
First 48 h: 60 mg Q12 and Maintenance dose: 54 mg Q12 h, patient with CLcr = 30 mL/min  
First 48 h: 80 mg Q24 and Maintenance dose: 70 mg Q24 h, patient with CLcr = 20 mL/min  
First 48 h: 67 mg Q24 and Maintenance dose: 54 mg Q24 h, patient with CLcr = 15 mL/min  
First 48 h: 60 mg Q24 and Maintenance dose: 35 mg Q24 h, patient with CLcr = 10 mL/min | \( C_{\text{max}} \leq 6 \text{ mg/L} \) and average concentrations within a dosing interval \( \leq 4 \text{ mg/L} \) |
| Hennig S [34] | NONMEM 7.2 | 2 compartments | Advanced internal (bootstrap, \( n = 300 \)) | 11 mg/kg/day for Cystic Fibrosis patients |                                                                                          | \( C_{\text{max}} \leq 20 \text{ mg/L} \) (relating to a 1-h peak/MIC ratios of 20/2)  
and \( C_{\text{min}} \leq 1 \text{ mg/L} \) |

AUC, area under the concentration–time curve; CLcr, creatinine clearance; \( C_{\text{max}} \), maximum concentration; \( C_{\text{min}} \), 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 \( C_{\text{max}} \geq 10 \times \text{MIC} \) by different MIC and aminoglycoside dose. \(^c\) PK parameters were calculated using Sawchuk–Zaske method.
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 Tables S2 and S3 (Supplementary Materials) for single- and two-compartmental models, respectively.

![Image of Figure 2](image-url)

**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).

3.6. Random Effect Modeling

Interindividual variability (IIV) for the main PK parameters was estimated only in one-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 $\omega^2$ (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 Tables S2 and S3 (Supplementary Materials), 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], 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 medians (ranges) using a mixed model were 24.3% (19.4–32%) and 0.056 mg/L (3.81 $\times$ 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 S4 (Supplementary Materials) 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, 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 $\mu$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 19 articles selected in this review for all three aminoglycosides, 12 (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 12 studies included at least a target related to $C_{\text{max}}$, while half of them also included a target related to $\text{AUC}_{0-24}$ or $\text{AUC}_{0-48}$, 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 $C_{\text{max}}$/MIC $\geq$ 8, $\text{AUC}_{0-24}$/MIC $\geq$ 75, and $C_{\text{min}}$ $\leq$ 2.5 mg/L [16–18]. For gentamicin, main PK/PD targets were $C_{\text{max}}$/MIC between 8 and 10, considering an MIC ranging from 1 to 2 mg/L [23–27].
As for tobramycin, $C_{\text{max}}$ values were targeted to be within 6 mg/L and 20 mg/L considering an MIC of 1 to 2 mg/L and $C_{\text{min}}$ values were set to be $\leq$1 mg/L [32–34].

4. Discussion

To treat severe infections, the administration of aminoglycosides in special populations has led to an increase in interest in aminoglycoside pharmacokinetics. Noticeably, a considerable number 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 in 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 two-compartment models ($n = 11$). In fact, Marsot et al. suggested in their review that single-compartment models could lead to an inaccurate estimation of aminoglycoside $V_d$ [15]. Although median CL and $V_d$ values were comparable across aminoglycosides, as shown in Figure 2, the parameter values tended to vary from one 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, such as acute kidney injury (AKI) or, conversely, augmented renal clearance (ARC). Although ARC is expected to being 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 a similar dosing regimen, median CL values for all three drugs in this present study were generally lower as compared to values in healthy volunteers: 6.48 L/h, 4.03 L/h, and 7.02 L/h for amikacin, gentamicin, and tobramycin, respectively [37–40]. As shown in Figure 2b, the median $V_d$ values for all three drugs in this review were higher than values shown in healthy volunteers: 16.15 L, 13.3 L/70 kg, 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 aminoglycoside pharmacokinetics. To better understand the inter- and intra-variability of aminoglycosides pharmacokinetics, the following covariates were the most retained in PopPK models: bodyweight ($n = 7$) and renal clearance ($n = 8$).

4.1.1. Renal Function

Among the 12 studies with normal renal function patients that performed a covariate analysis, seven studies included $CL_{CR}$ calculated using the Cockcroft–Gault equation ($CL_{CG}$) in order to better estimate values of CL or $V_d$ [16,18,19,23,25,32,33]. To illustrate the impact of $CL_{CR}$ on aminoglycoside CL, we plotted aminoglycoside CL against this covariate according to the values and model equations reported by the studies that included $CL_{CR}$ (Figure 3). This plot shows 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, therefore, also considered in the estimation of aminoglycoside CL or $V_d$. 
Figure 3. (a) Aminoglycoside clearance values against range of creatinine clearance in the respective studies. (b) Aminoglycoside volume of distribution values against range of bodyweight in the respective studies. Note: Two studies used IBW [19,26] and one used TBW [24] in their model.

Although $CL_{CG}$ seems to be frequently used in guidelines [41], it might not represent the most accurate way of estimating aminoglycoside 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 suggested that $CL_{CG}$ should not 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, the aminoglycoside elimination pathway mainly involves 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 the 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.

Despite age not being a significant covariate in the estimation of aminoglycoside PK parameters in ICU patients, except when considered in the CG equation, 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 [50]. In fact, it has been suggested that gentamicin renal clearance seemed to
decline more significantly after reaching 60 to 70 years of age [51]. 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 Vd 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 [51–53].

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, e.g., aminoglycosides [54]. Therefore, administration of higher doses to reach targeted serum concentrations is needed. In several studies presented in this review, patient 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 aminoglycoside 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 aminoglycoside Vd. As mentioned earlier, bodyweight also has an influence on the estimation of the CLCR, especially if CLCG is used. All seven studies that included CLCG 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 in amikacin, gentamicin, and tobramycin models, respectively [16,29,34]. In fact, these three covariates were retained in the estimation of aminoglycoside Vd. Although BSA has rarely been mentioned as a covariate influencing aminoglycoside PK, it was suggested by Boidin et al. that the use of BSA might lower the risk of exposure in overweight patients [16,55]. In fact, BSA considers both the bodyweight and height, where the latter is much less variable than bodyweight in ICU adult patients [56]. Recent studies did suggest dose recommendations based on height (mg/cm) instead of bodyweight for tobramycin in cystic fibrosis patients [57,58].

Although the inclusion of parameters related to bodyweight or body size in the final model of most studies allowed a reduction in 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 [59,60].

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. Different strategies and steps are possible in order to adequately evaluate models from the literature. For more information on these strategies, refer to the Supplementary Materials.

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 in adequate bias and inaccuracy values. Although each of these three models was 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 number of studies performing it is rather insufficient [61]. 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 [62–64], thus suggesting that a certain challenge still remains.

The conception of a meta-model for each aminoglycoside may also be feasible by including the characteristics (covariates, error models, initial estimates) from the best-performing models following external validation with an independent dataset. The development of this meta-model is, therefore, derived from the independent dataset while also being based on previously published PK models.

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 $C_{\text{max}} \geq 64 \text{ mg/L}$ and $\text{AUC}_{0-24} \geq 600 \text{ mg*h/L}$ compared to the conventional 30 mg/kg of corrected bodyweight (CBW), considering an MIC of 8 mg/L [16]. It was suggested that an increase in the dosing interval up to 36 or 48 h might be feasible in critically ill patients with normal to moderate renal function. In fact, several recommendations were simulated on the basis of different values of the two significant covariates in their respective PopPK model, $\text{CL}_{\text{CG}}$ (10 mL/min to 250 mL/min), and BSA (1.5 m² to 2.5 m²). As for Arechiga-Alvarado et al., different daily dosing recommendations were simulated on the basis of three different MICs (4 mg/L, 8 mg/L, and 16 mg/L) and $\text{CL}_{\text{CR}}$ ranging from 60 mL/min to 200 mL/min [19]. Considering an 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 $\text{CL}_{\text{CR}}$ 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 h and a dose ranging from 25 mg/kg and 30 mg/kg every 36 to 48 h were the most appropriate in order to maximize TAR for $C_{\text{max}}/\text{MIC} \geq 8$ and $\text{AUC}_{0-24} \geq 70$ or $\text{AUC}_{0-24} \geq 75$ with an 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 an 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 $C_{\text{max}} > 10 \text{ mg/L}$, $C_{\text{trough at 24h}} < 1 \text{ mg/L}$, and $\text{AUC}$ between 80 and 125 mg*h/L according to different fixed dose regimens [32]. Their main takeaway was 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 $\text{AUC}_{48}$ with daily fixed dosages of 375 and 400 mg. The other study from Aarons et al. simulated dosing regimens on the basis of $\text{CL}_{\text{CR}}$ values [33]. All dosing regimens proposed were presented as a sequence: a fixed dose administered for the first 48 h with a dosing interval ranging from 8 h to 24 h depending on the $\text{CL}_{\text{CR}}$. Following the first 48 h, a maintenance dose was to be administered as per the same dosing interval. The first period of 48 h was chosen according to the authors’ assumption that aminoglycoside concentration was to be detectable and, thus, have the possibility of dose adaptation [33]. As for patients under RRT, Teigen et al. demonstrated that, on the basis of PK/PD targets of $C_{\text{max}} \geq 8 \text{ mg/L}$ and $\text{AUC}_{48}$ between 140 and 24 0 mg*h/L, three fixed starting doses (300 mg, 240 mg, 220 mg) prior to dialysis are 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 48 h and administered 30 min prior to RRT (EDD-f in this situation) was able to achieve PK/PD targets compared to daily 7 mg/kg administration [27].
Among the articles that performed simulation of dosing regimens, five of them simulated optimal dosing regimens interpolated from the actual dose administered in their respective study populations [17,18,24–26], whereas the other three resulted in optimal dosing regimens extrapolated from the actual dosing regimen administered [16,19,34]. Results from simulations based on inter- and extrapolation should be interpreted cautiously considering the high variability observed in the estimation of PK parameters for all aminoglycosides.

5. Conclusions

Although many PopPK models for aminoglycosides exist in the literature, important variability remains. Despite multiple covariates being tested across all studies, the significant covariates would still be creatinine clearance and bodyweight for aminoglycoside clearance and volume of distribution, respectively. Moreover, considering that aminoglycoside-induced toxicity is reported to be more frequent amongst individuals with mitochondrial DNA mutations, such as m.1555A>G and m.1494C>T in the 12S rRNA gene [65], pharmacogenetics should be taken into account in future PopPK models. Several limitations are to be considered; seven study populations had fewer than 30 subjects, and more than half of the articles had retrospective designs with few aminoglycoside samples.

Although simulations have been carried out and help us to suggest optimal dosages, it should not be forgotten that many models were not 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 aminoglycoside individualized dosing. TDM remains essential in the ICU population to achieve therapeutic success while minimizing the likelihood of toxicity.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/antibiotics10050507/s1: Table S1. Checklist of information to be included when reporting a clinical pharmacokinetic study based on ClinPK. Table S2. Characteristics of the population pharmacokinetic models developed by the studies included in this review. (one compartment). Table S3: Characteristics of the population pharmacokinetic models developed by the studies included in this review (two-compartment). Table S4. Covariates that were included or evaluated for inclusion by the population pharmacokinetic models included in this review.

Author Contributions: Conceptualization, A.D., Y.L.W. and A.M.; methodology, A.D., Y.L.W., and A.M.; data analysis, A.D.; writing—original draft preparation, A.D. and Y.L.W., writing—review and editing, A.D., C.S., Y.L.W., D.W. and A.M., supervision, A.M. All authors read and agreed to the published version of the manuscript.

Funding: Amélie Marsot received funding from the Réseau Québécois de Recherche sur les Médicaments (RQRM) and received salary support from the Fonds de Recherche Santé Québec (FRQS).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: Alexandre Duong, Chantale Simard, David Williamson, Yi Le Wang, and Amélie Marsot declare no conflicts of interest.

References

1. Krause, K.M.; Serio, A.W.; Kane, T.R.; Connolly, L.E. Aminoglycosides: An Overview. *Cold Spring Harb. Perspect. Med.* 2016, 6, a027029. [CrossRef] [PubMed]
2. Mingeot-Leclercq, M.-P.; Glupczynski, Y.; Tulkens, P.M. Aminoglycosides: Activity and Resistance. *Antimicrob. Agents Chemother.* 1999, 43, 727. [CrossRef] [PubMed]
3. Dombrovskiy, V.Y.; Martin, A.A.; Sunderram, J.; Paz, H.L. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit. Care Med.* 2007, 35, 1244–1250. [CrossRef]
4. Buik, S.; Mouton, J.; Gysens, I.; Verbrugh, H.; Bruniuing, H. Experience with a once-daily dosing program of aminoglycosides in critically ill patients. Intens Care Med. 2002, 28, 936–942. [CrossRef] [PubMed]

5. Leekha, S.; Terrell, C.L.; Edson, R.S. General principles of antimicrobial therapy. Mayo Clin. Proc. 2011, 86, 156–167. [CrossRef]

6. Bland, C.M.; Pai, M.P.; Lodise, T.P. Reappraisal of Contemporary Pharmacokinetic and Pharmacodynamic Principles for Informing Aminoglycoside Dosing. Pharmacotherapy. J. Hum. Pharmacol. Drug Ther. 2018, 38, 1229–1238. [CrossRef]

7. Craig, W.A. Optimizing Aminoglycoside Use. Crit. Care Clin. 2011, 27, 107–121. [CrossRef]

8. Eliopoulos, G.M.; Drusano, G.L.; Ambrose, P.G.; Bhavnani, S.M.; Bertino, J.S.; Nafziger, A.N.; Louie, A. Back to the Future: Using Aminoglycosides Again and How to Dose Them Optimally. Clin. Infect. Dis. 2007, 45, 753–760. [CrossRef]

9. Germovsek, E.; Barker, C.I.; Sharland, M. What do I need to know about aminoglycoside antibiotics? Arch. Dis. Child.-Educ. Pract. Ed. 2017, 102, 89. [CrossRef]

10. Kumar, A.; Roberts, D.; Wood, K.E.; Light, B.; Parrillo, J.E.; Sharma, S.; Suppes, R.; Feinstein, D.; Zanotti, S.; Taiberg, L.; et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit. Care Med. 2006, 34, 1589–1596. [CrossRef]

11. de Velde, F.; Mouton, J.W.; de Winter, B.C.M.; van Gelder, T.; Koch, B.C.P. Clinical applications of population pharmacokinetic models of antibiotics: Challenges and perspectives. Pharmacol. Res. 2018, 134, 280–288. [CrossRef]

12. Lovern, M.; Sargentini-Maier, M.-L.; Otoul, C.; Watelet, J.-B. Population pharmacokinetic and pharmacodynamic analysis in allergic diseases. Drug Metab. Rev. 2009, 41, 475–485. [CrossRef] [PubMed]

13. Kanji, S.; Hayes, M.; Ling, A.; Shamsaeer, L.; Chant, C.; Edwards, D.J.; Edwards, S.; Ensom, M.H.H.; Foster, D.R.; Hardy, B.; et al. Reporting Guidelines for Clinical Pharmacokinetic Studies: The ClinPK Statement. Clin. Pharmacokinet. 2015, 54, 783–795. [CrossRef] [PubMed]

14. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009, 6, e1000097. [CrossRef] [PubMed]

15. Marso, A.; Guilhaumou, R.; Riff, C.; Blin, O. Amikacin in Critically Ill Patients: A Review of Population Pharmacokinetic Studies. Clin. Pharmacokinet. 2017, 56, 127–138. [CrossRef] [PubMed]

16. Boidin, C.; Bourguignon, L.; Cohen, S.; Roger, C.; Lefrant, J.-Y.; Roberts, J.A.; Allaouchiche, B.; Lepape, A.; Friggeri, A.; Goutelle, S. Amikacin Initial Dose in Critically Ill Patients: A Nonparametric Approach To Optimize a Priori Pharmacokinetic/Pharmacodynamic Target Attainments in Individual Patients. Antimicrob. Agents Chemother. 2019, 63, e00993-19. [CrossRef] [PubMed]

17. Roger, C.; Wallis, S.C.; Muller, L.; Saiissi, G.; Lipman, J.; Lefrant, J.-Y.; Roberts, J.A. Influence of Renal Replacement Modalities on Amikacin Population Pharmacokinetics in Critically Ill Patients on Continuous Renal Replacement Therapy. Antimicrob. Agents Chemother. 2016, 60, 4901. [CrossRef]

18. Carrié, C.; Delzor, F.; Roure, S.; Dubuisson, V.; Petit, L.; Molimard, M.; Breilh, D.; Biais, M. Population Pharmacokinetic Study of the Suitability of Standard Dosing Regimens of Amikacin in Critically Ill Patients with Open-Abdomen and Negative-Pressure Wound Therapy. Antimicrob. Agents Chemother. 2020, 64, e02098-19. [CrossRef] [PubMed]

19. Aréchiga-Alvarado, N.A.; Medellín- Garibay, S.E.; Milán-Segovia, R.d.C.; Ortiz-Álvarez, A.; Magaña-Aquino, M.; Romano-Moreno, S. Population Pharmacokinetics of Amikacin Administered Once Daily in Patients with Different Renal Functions. Antimicrob. Agents Chemother. 2020, 64, e02178-19. [CrossRef] [PubMed]

20. Petitcollin, A.; Dequín, P.F.; Darrouzain, F.; Vecellio, L.; Biais, M.C.; Nunguiane, G.; Lang, C.N.; Beirão, J.C.; Mathot, R.A.A.; van Hest, R.M. Determinants of gentamicin concentrations in critically ill patients: A population pharmacokinetic analysis. Int. J. Antimicrob. Agents. 2017, 49, 204–211. [CrossRef] [PubMed]

21. French, M.A.; Cerra, F.B.; Plaut, M.E.; Schentag, J.J. Amikacin and gentamicin accumulation pharmacokinetics and nephrotoxicity in critically ill patients. Antimicrob. Agents Chemother. 1981, 19, 147–152. [CrossRef] [PubMed]

22. Hodiamont, C.J.; Juffermans, N.P.; Bouman, C.S.C.; de Jong, M.D.; Mathôt, R.A.A.; van Hest, R.M. Determinants of gentamicin concentrations in critically ill patients: A population pharmacokinetic analysis. Int. J. Antimicrob. Agents. 2017, 49, 204–211. [CrossRef] [PubMed]

23. Teigen, M.M.B.; Duffull, S.; Dang, L.; Johnson, D.W. Dosing of Gentamicin in Patients with End-Stage Renal Disease Receiving Hemodialysis. J. Clin. Pharmacol. 2006, 46, 1259–1267. [CrossRef] [PubMed]

24. Rea, R.S.; Capitano, B.; Bies, R.; Bigos, K.L.; Smith, R.; Lee, H. Suboptimal Aminoglycoside Dosing in Critically Ill Patients. Ther. Drug Monit. 2008, 30, 674–681. [CrossRef] [PubMed]

25. Bos, J.C.; Prins, J.M.; Misticio, M.C.; Nunguiane, G.; Lang, C.N.; Beirão, J.C.; Mathôt, R.A.A.; van Hest, R.M. Population Pharmacokinetics with Monte Carlo Simulations of Gentamicin in a Population of Severely Ill Adult Patients from Sub-Saharan Africa. Antimicrob. Agents Chemother. 2019, 63, e02328-18. [CrossRef] [PubMed]

26. Hodiamont, C.J.; Janssen, J.M.; de Jong, M.D.; Mathôt, R.A.; Juffermans, N.P.; van Hest, R.M. Therapeutic Drug Monitoring of Gentamicin Peak Concentrations in Critically Ill Patients. Ther. Drug Monit. 2017, 39, 522–530. [CrossRef]

27. Roberts, J.A.; Field, J.; Visser, A.; Whitbread, R.; Tallot, M.; Lipman, J.; Kirkpatrick, C.M.J. Using population pharmacokinetics to determine gentamicin dosing during extended daily dialfiltration in critically ill patients with acute kidney injury. Antimicrob. Agents Chemother. 2010, 54, 3635–3640. [CrossRef] [PubMed]

28. Barletta, J.F.; Johnson, S.B.; Nix, D.E.; Nix, L.C.; Erstad, B.; L. Population Pharmacokinetics of Aminoglycosides in Critically Ill Trauma Patients on Once-Daily Regimens. J. Trauma Acute Care Surg. 2000, 49, 869–872. [CrossRef] [PubMed]
56. Schneider, A.G.; Baldwin, I.; Freitag, E.; Glassford, N.; Bellomo, R. Estimation of fluid status changes in critically ill patients: Fluid balance chart or electronic bed weight? *J. Crit. Care* **2012**, *27*, e745.e7–e745.e712. [CrossRef]

57. Alghanem, S.S.; Touw, D.J.; Thomson, A.H. Pharmacokinetic/pharmacodynamic analysis of weight- and height-scaled tobramycin dosage regimens for patients with cystic fibrosis. *J. Antimicrob. Chemother.* **2019**, *74*, 2311–2317. [CrossRef]

58. Crass, R.L.; Pai, M.P. Optimizing Estimated Glomerular Filtration Rate to Support Adult to Pediatric Pharmacokinetic Bridging Studies in Patients with Cystic Fibrosis. *Clin. Pharmacokinet.* **2019**, *58*, 1323–1332. [CrossRef]

59. Maskin, L.P.; Attie, S.; Setten, M.; Rodriguez, P.O.; Bonelli, I.; Stryjawski, M.E.; Valentini, R. Accuracy of Weight and Height Estimation in an Intensive Care Unit. *Anaesth. Intensive Care* **2010**, *38*, 930–934. [CrossRef]

60. Bloomfield, R.; Steel, E.; MacLennan, G.; Noble, D.W. Accuracy of weight and height estimation in an intensive care unit: Implications for clinical practice and research. *Crit. Care Med.* **2006**, *34*, 2153–2157. [CrossRef]

61. Brendel, K.; Comets, E.; Laffont, C.; Mentré, F. Evaluation of different tests based on observations for external model evaluation of population analyses. *J. Pharm. Pharm.* **2010**, *37*, 49–65. [CrossRef] [PubMed]

62. Guo, T.; van Hest, R.M.; Roggeveen, L.F.; Fleuren, L.M.; Thoral, P.J.; Bosman, R.J.; van der Voort, P.H.J.; Girbes, A.R.J.; Mathot, R.A.A.; Elbers, P.W.G. External Evaluation of Population Pharmacokinetic Models of Vancomycin in Large Cohorts of Intensive Care Unit Patients. *Antimicrob. Agents Chemother.* **2019**, *63*, e02543-18. [CrossRef] [PubMed]

63. Wang, Y.L.; Guilhaumou, R.; Blin, O.; Velly, L.; Marsot, A. External evaluation of population pharmacokinetic models for continuous administration of meropenem in critically ill adult patients. *Eur. J. Clin. Pharmacol.* **2020**, *76*, 1281–1289. [CrossRef]

64. Bukkems, L.H.; Rooger, C.; Hodiamont, C.J.; Lefrant, J.-Y.; Juffermans, N.P.; Roberts, J.A.; van Hest, R.M. Predictive performance of a gentamicin population pharmacokinetic model in two western populations of critically ill patients. *Int. J. Antimicrob. Agents* **2018**, *52*, 218–225. [CrossRef] [PubMed]

65. Gao, Z.; Chen, Y.; Guan, M.-X. Mitochondrial DNA mutations associated with aminoglycoside induced ototoxicity. *J. Otol.* **2017**, *12*, 1–8. [CrossRef]