Université de Montréal

Pharmacothérapie de précision des aminosides en unités de soins intensifs

Par
Alexandre Duong

Faculté de Pharmacie

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Pharmacothérapie de précision des aminosides en unités de soins intensifs

Présenté par

Alexandre Duong

A été évalué par un jury composé des personnes suivantes

Davide Brambila
Président-rapporteur

Amélie Marsot
Directeur de recherche

Sonia Khier
Examinateur externe

Résumé

Les aminosides sont majoritairement utilisés pour le traitement d'infections causées par des bactéries Gram-négatif. En raison de leur index thérapeutique étroit, les aminosides doivent être administrés avec des doses adéquates afin d'optimiser la guérison clinique tout en minimisant les risques de toxicité. De plus, le suivi thérapeutique posologique est d'autant plus important pour les populations spéciales. En effet, ces dernières, telles que les patients aux soins intensifs, peuvent présenter des conditions physiopathologiques pouvant influencer la pharmacocinétique des aminosides. Ce projet, séparé en trois volets, a permis la description des habitudes de posologies et de suivi thérapeutique des aminosides auprès des patients aux soins intensifs du Québec à l'aide d'un questionnaire. De plus, ce projet inclut également une revue des modèles pharmacocinétiques par approche populationnelle (PopPK) des aminosides pour des patients aux soins intensifs. Finalement, ce projet consiste en l'évaluation de la performance prédictive des modèles de gentamicine avec une base de données-patients provenant de deux établissements de santé du Québec. Le volet 1, sous forme d'un questionnaire, a obtenu un taux de réponse de 64.7%, représentant 42% des lits aux soins intensifs de la province. Les régimes posologiques administrés de façon uniquotidienne, sont plus utilisés que l'administration multiquotidienne avec des doses allant de 5 à 7 mg/kg pour la gentamicine et la tobramycine. L'amikacine est très peu utilisé dans les établissements du Québec. Les cibles thérapeutiques respectaient généralement les cibles recommandées dans la littérature. Le volet 2 a permis la description de six, onze et cinq modèles PopPK d'amikacine, de gentamicine et de tobramycine respectivement. Les modèles à deux compartiments décriraient mieux la pharmacocinétique de l'amikacine et de la tobramcyine, tandis que les modèles à un compartiment décriraient mieux la pharmacocinétique de la gentamicine. Les covariables les plus souvent considérées comme significatives étaient la clairance rénale et le poids corporel. Dans le volet 3, malgré qu'une performance prédictive adéquate a été déterminée auprès des 4 modèles évaluées avec la base de données-patients du Québec, de la variabilité demeure présente concernant la prédiction des concentrations et l'application de ces modèles dans un contexte doit ainsi se faire avec prudence. À partir du meilleur modèle, des régimes posologiques *a priori* ont pu être simulés.

Mots-clés : Aminosides, modélisation pop-PK, soins intensifs, adaptation posologique

Abstract

Aminoglycosides are mostly used for treatment of severe Gram-negative infections. Due to their narrow therapeutic index, aminoglycosides should be administered following adequate dosing regimens in order to optimize clinical efficacy while minimizing the risks of toxicity. Moreover, therapeutic drug monitoring is even more important for frail populations such as the critically ill patients. In fact, the latter often present pathophysiological changes that may influence aminoglycosides' pharmacokinetics. This project was divided in three parts. Firstly, a survey was developed to describe the usual dosing and monitoring practices of aminoglycosides in critically ill patients in the province of Quebec. This project also includes a literature review of aminoglycosides population pharmacokinetic (PopPK) models in critically ill patients. Finally, this project also consists of evaluating the predictive performance of gentamicin PopPK models with a validation dataset composed of patients from two Quebec institutions. The survey had a response rate of 64.7%, therefore representing 42% of all intensive care unit beds in the province. Once-daily-dose regimens are more used than multiple-daily-dose regimens. Most common gentamicin and tobramycin administered dose regimens ranged from 5 to 7 mg/kg. Amikacin is rarely used in Quebec's institutions. Therapeutic targets were generally in-line with findings from the literature. The literature review described six, eleven and five amikacin, gentamicin and tobramycin PopPK models, respectively. Amikacin and tobramycin pharmacokinetics were mostly described by bi-compartment models whereas gentamicin pharmacokinetics were mostly described by single-compartment model. Most common covariates used were renal clearance and bodyweight. In the third part of this project, although an adequate predictive performance was determined in all four evaluated models, variability in the predicted concentrations by the model still remains. Therefore, usage of these models in clinical settings should be done cautiously. Based on the best performing model, *a priori* dosing regimens were simulated.

Keywords : Aminoglycosides, Pop-PK modeling, critically ill patients, dose adaptation

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AUC: Aire sous la courbe

C_{max} : Concentration maximale

CMI: Concentration minimale inhibitrice

EUCAST: European Committee on Antmicrobial Susceptibility Testing

H : heure(s)

HSCM : Hôpital Sacré-Cœur de Montréal

GOF: Goodness of Fit

IUCPQ : Institut Universitaire de Cardiologie et Pneumologie de Québec

L : litre(s)

MADPE: Médiane absolue de l'erreur de prédiction

MDD : Multiple-daily-dosing

MDPE: Médiane de l'erreur de prédiction

Mg/kg: milligramme par kilogramme

MIPD: model-informed precision dosing

NPDE *:* normalized prediction distribution error

ODD : Once-daily-dosing

PE: Erreur de prédiction

PK/PD : Pharmacocinétique/pharmacodynamie

PopPK : Pharmacocinétique de population

STP^2 : Laboratoire Suivi Thérapeutique Pharmacologique & Pharmacocinétique

SPP: Species plural

USCAST : United States Committee on Antimicrobial Susceptibility Testing

À mes grands-parents 楊財增 et 陳秀蓮, 陳萬俊 et 許玉姬,

À mes parents Ngi et Hue

À Linda

Shinzou Wo Sasageyo !
[Dedicate your hearts!]
Erwin Smith, Shingeki No Kyojin

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Chapitre 1 – INTRODUCTION

Aminosides

Pharmacologie

La première molécule de la famille des aminosides, la streptomycine, a été découverte en 1944. À travers les décennies suivantes, d'autres membres de la famille des aminosides ont également été introduits, tels que la gentamicine, la tobramycine et l'amikacine (1). La structure moléculaire des aminosides est habituellement composée d'un noyau central s'y rattachant des sucres aminés par des liens glycosidiques. Grâce aux propriétés de la structure moléculaire des aminosides, ces derniers peuvent se lier, de façon irréversible, à la sous-unité 30S du ribosome bactérien afin d'interférer partiellement ou complètement avec la synthèse des protéines bactériennes (Figure 1. – . À ce jour, la gentamicine ainsi que d'autres molécules de la famille des aminosides sont considérées comme des anti-microbiens ayant un large spectre d'activité, notamment en raison de leur utilisation dans le traitement d'infections de type Gram-négatif ou leur utilisation en synergie contre certaine bactéries Gram-positif. Ainsi, les aminosides sont utilisés pour plusieurs indications telles que les endocardites infectieuses, les infections urinaires, la septicémie et les exacerbations pulmonaires aigues en fibrose kystique (2).

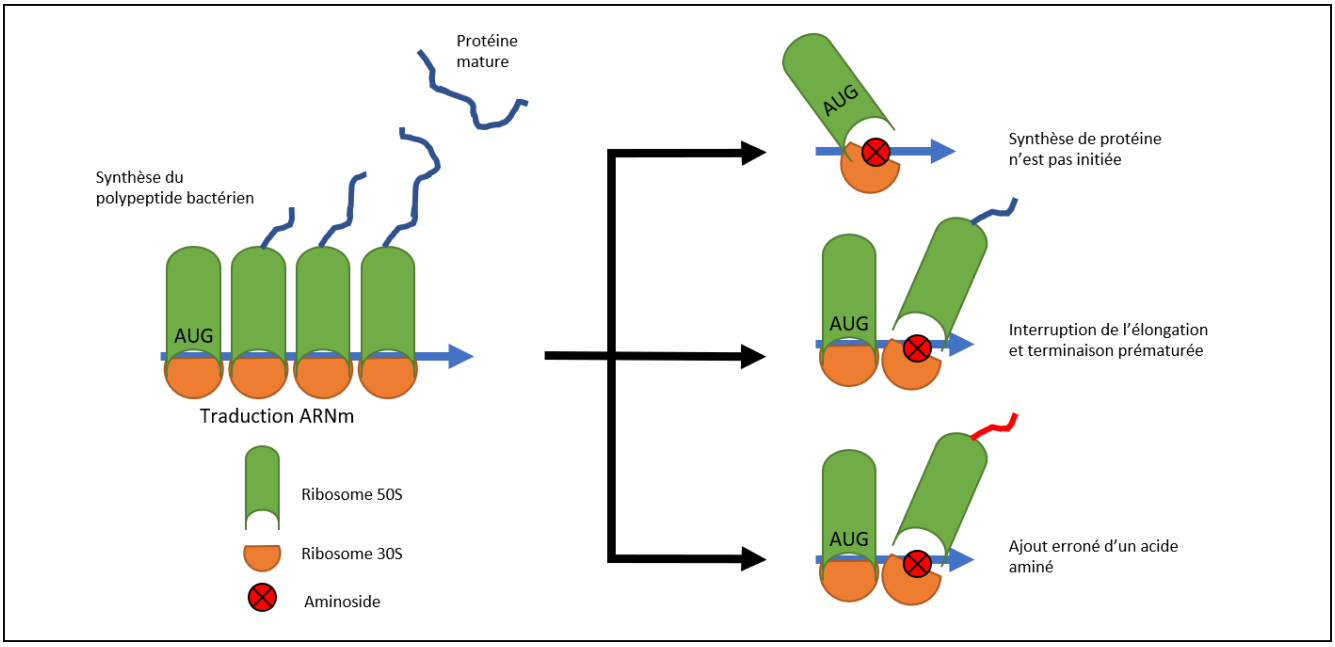

Figure 1. – Mécanisme d'action des aminosides et impacts sur la synthèse de protéines bactériennes.

Figure adaptée de Ahmed, S., Sony, S.A., Chowdhury, M.B. et al. Retention of antibiotic activity against resistant bacteria harbouring aminoglycoside-N-acetyltransferase enzyme by adjuvants: a combination of in-silico and in-vitro study. *Sci Rep 10, 19381 (2020) (*3*).*

Pharmacocinétique/Pharmacodynamie (PK/PD)

Considérant la faible absorption des aminosides au niveau gastro-intestinal, ces derniers sont principalement administrés de façon intraveineuse ou intramusculaire (4). En raison de leurs propriétés hydrophiles, les aminosides se distribuent principalement dans les fluides extracellulaires et présentent un volume de distribution de 15 à 17 L (5). Étant donné que les aminosides sont rapidement éliminés par filtration glomérulaire, leur temps de demi-vie au niveau plasmatique, est d'environ 2 heures, mais peut atteindre 30 à 60 heures pour un patient d'une insuffisance rénale sévère.

L'efficacité clinique des aminosides dépend d'une activité concentration-dépendante telle que présentée à la Figure 2. – . Cette activité bactéricide nécessite que le ratio de la concentration maximale (C_{max}) ou l'aire sous la courbe (AUC) sur la concentration minimale inhibitrice (CMI) de la bactérie en question, soit supérieure ou égale à une certaine valeur. S'ajoutant aux

mécanismes mentionnés dans la (Figure 1. – , les aminosides sont également caractérisés par un effet post-antibiotique considérable permettant de réduire la fréquence d'administration (6).

Généralement, la cible C_{max}/CMI est utilisée afin d'assurer la guérison clinique dans plusieurs indications. Par exemple, lors d'un traitement contre une endocardite à bactérie Gram-positive, à entérocoques ou streptocoques, la gentamicine est souvent utilisée en synergie avec une bêta-lactamine ou un glycopeptide. Cette infection grave pouvant être associée à un sepsis nécessite un ratio de C_{max}/CMI supérieur ou égale à 10 (7). De plus, afin de favoriser la guérison clinique dues à des infections sévères (septicémie) tout en prévenant la résistance antimicrobienne, la cible C_{max}/CMI devrait être supérieure ou égale à 8 ou 10, pour des valeurs de CMI allant de 1 à 2 mg/L pour *Staphylococcus species plural (spp), Pseudomonas spp* et *Enterococcus spp* en fonction des valeurs fournies par les agences United States Committee on Antimicrobial Susceptibility Testing (USCAST) et European Committee on Antmicrobial Susceptibility Testing (EUCAST) (8, 9).

Bien que la cible C_{max}/CMI semble être la plus utilisée en pratique clinique, plusieurs études ont suggéré que la cible AUC/CMI serait une mesure plus adéquate de l'exposition et de l'efficacité du traitement antimicrobien (10). En effet, en plus de mesurer les pics de gentamicine et de tobramycine, les lignes directrices australiennes recommandent également que l'AUC dans les premières 24 heures (AUC_{0-24}) devrait se situer entre 80 et 100 mg*h/L, en considérant une valeur de CMI de 1 mg/L pour les bactéries Gram-négatif (11).

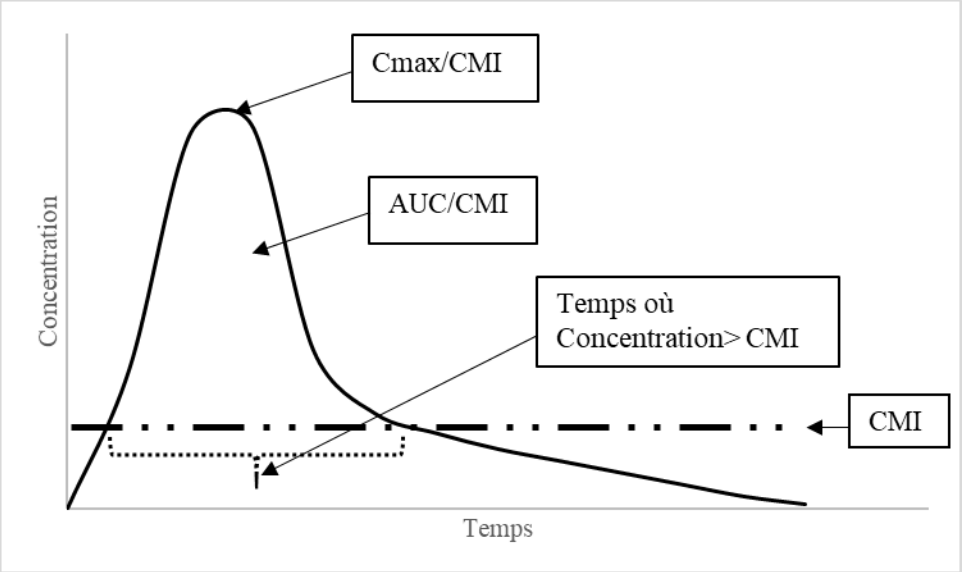

Figure 2. – Caractéristiques PK/PD présentées sur une courbe de concentration en fonction du temps.

$C_{max:}$ Concentration Maximale, AUC : Aire sous la courbe, CMI : Concentration minimale inhibitrice, C_{max}/CMI : Ratio entre la concentration maximale et la CMI; AUC/CMI : Ratio entre l'aire sous la courbe et la CMI; Temps > CMI : Intervalle de temps à laquelle la concentration demeure supérieure à la CMI.

Figure adaptée de Roberts, Jason A. B Pharm (Hons); Lipman, Jeffrey FJFICM, MD *Pharmacokinetic issues for antibiotics in the critically ill patient, Critical Care Medicine*: March 2009 - Volume 37 - Issue 3 - p 840-851 (12).

Toxicité

Malgré que les aminosides soient rapidement filtrés par filtration glomérulaire, ces derniers se retrouvent également à s'accumuler au niveau du cortex rénal, et par le fait même, peuvent présenter des risques de néphrotoxicité (2). De plus, l'administration répétée de doses élevées d'aminosides peut également engendrer de l'ototoxicité, c'est-à-dire, des répercussions irréversibles au niveau de l'appareil auditif (13). En raison de ces signes de toxicité connus, les aminosides sont considérés comme des molécules ayant un index thérapeutique. Ainsi, non seulement les C_{max} ou l'AUC doivent être surveillés afin de s'assurer une efficacité clinique adéquate, mais le suivi thérapeutique posologique doit également tenir en compte les concentrations pré-doses. En effet, ces dernières aussi connues sous le nom de creux, devraient idéalement être inférieures à 0.5 ou 1 mg/L avant la prochaine administration d'aminoside (14).

Régimes posologiques

Deux types de régimes posologiques sont couramment utilisés pour l'administration des aminosides. La première est l'approche traditionnelle aussi connue sous le nom de *multiple-daily-dosing* (MDD). Cette dernière, notamment prédominante à la fin du 20^{e} siècle, consiste à administrer les aminosides plusieurs fois par jour (15). En revanche, au fil des décennies suivantes, une nouvelle approche a été proposée et consistait à administrer les aminosides une seule fois par jour. Cette nouvelle méthode d'administration appelée *once-daily-dosing* (ODD) permettait notamment de réduire les risques de toxicité rénale ainsi que l'ototoxicité tout en maintenant l'efficacité clinique démontrée par l'approche traditionnelle (15). En effet, cette méthode accentuerait également l'effet post-antibiotique des aminosides et réduirait la résistance adaptative des bactéries (15).

En raison de l'apparition de ces données probantes au niveau des avantages de cette nouvelle approche, aussi connue sous le nom d'*extended-interval dosing*, une augmentation de l'utilisation de l'administration uniquotidienne a été remarquée auprès établissements de santé américaines (16, 17).

Adaptation et suivi thérapeutique

Étant donné l'élimination rénale des aminosides et de la possibilité de néphrotoxicité, l'adaptation et le suivi posologique sont primordiaux. Ainsi, pour remédier à cette situation, plusieurs nomogrammes ont été développés, dont ceux de Hartford et d'Urban et Craig (7, 18). Malgré une utilisation répandue de ces nomogrammes, ces derniers ne sont pas toujours adaptés à certaines populations spéciales (19-21). De plus, les doses recommandées peuvent également ne plus correspondre à ce qui peut être utilisées aujourd'hui.

Population aux soins intensifs

Caractéristiques démographiques

Les patients admis aux soins intensifs peuvent présenter des conditions pouvant influencer la pharmacocinétique et la pharmacodynamie des antibiotiques. En effet, dues à des infections bactériennes sévères, une réaction inflammatoire généralisée peut avoir lieu dans l'organisme. Cet état inflammatoire, appelé sepsis, engendre ainsi des changements hémodynamiques et des

défaillances au niveau de certains organes vitaux, tel que présenté à la Figure 3. – . En raison de ces modifications physiopathologiques sur l'organisme, le choc septique est considéré comme l'une des plus grandes causes de mortalité à travers le monde et son taux de mortalité est estimé aux alentours de 38% en Europe et en Amérique du Nord (22).

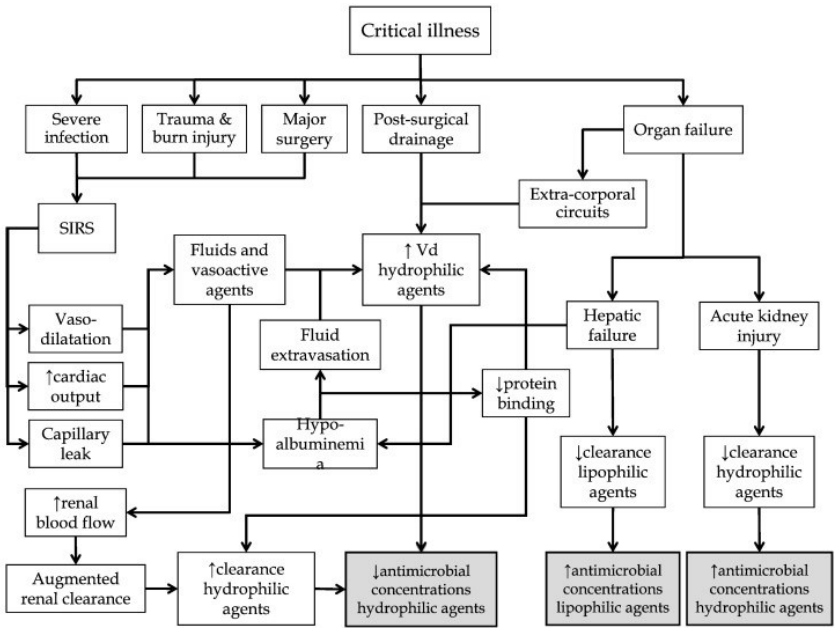

Figure 3. – Altérations physiopathologiques chez les patients aux soins intensifs et les effets sur la pharmacocinétique des agents antimicrobiens.

Figure tirée de Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents. *Advanced Drug Delivery Reviews.* 2014;77:3-11(23)

Adaptation posologique

Dans le cas des aminosides, étant donné que ces derniers sont des molécules hydrophiles, l'impact du choc septique serait associé à plusieurs modifications des paramètres PK dont une augmentation du volume de distribution et généralement une diminution de la clairance rénale, excepté auprès des patients sous dialyse, et ainsi une augmentation de la demi-vie d'élimination (23). Ainsi, dépendant de ces modifications pouvant être transitoires, du contexte clinique et des comorbidités d'un patient, un même dosage pourrait engendrer des concentrations sous-thérapeutiques ou toxiques. Par le fait même, cette grande variabilité inter- et intra-individuelle implique un défi au niveau de la détermination d'une dose optimale. De plus, l'administration du bon traitement à la

bonne dose est primordiale afin de maximiser les chances de guérison clinique, notamment chez les patients aux soins intensifs.

Modélisation pharmacocinétique de population

Concept

En 1977, Sheiner et al. introduit la modélisation pharmacocinétique qui a pour but de décrire les concentrations de médicaments à travers le temps afin d'estimer les paramètres pharmacocinétiques à partir d'équations mathématiques(24). Ces dernières permettent également d'inclure des paramètres additionnels afin de décrire les différentes sources de variabilité. De plus, l'impact, s'il y a lieu, des différents facteurs physiopathologiques sur les paramètres pharmacocinétiques populationnels peut être identifié et mesuré.

La modélisation pharmacocinétique par approche populationnelle (PopPK) ne nécessite pas nécessairement un grand nombre d'échantillons par individu ou que tous les individus aient les mêmes temps de prélèvement (25). En effet, l'estimation des paramètres pharmacocinétiques moyens dans une population est possible avec des données éparses (*sparse sampling*). Ce principe est un avantage, notamment dans le développement de modèles auprès de populations vulnérables où les prélèvements fréquents peuvent être un défi (25).

Applications

Grâce à la capacité d'estimer les paramètres pharmacocinétiques moyens d'une population tout en considérant les sources de variabilité, la modélisation PopPK permet également de prédire les concentrations attendues en fonction des caractéristiques individuelles de chaque patient. L'opposé est aussi possible, c'est-à-dire, la détermination de régimes posologiques à partir de simulations afin d'atteindre des concentrations thérapeutiques cibles (26). De plus, l'approche bayésienne ajoutée à la modélisation PopPK ouvre la porte à la médecine personnalisée (25). En effet, cette dernière vise à administrer le bon traitement, à la bonne dose au bon moment pour le bon patient.

En revanche, avant d'utiliser un modèle PopPK dans un contexte clinique réel, il est d'abord nécessaire d'évaluer les capacités prédictive ce modèle dans une population cible afin d'effectuer des simulations ou des adaptations de posologie. Cette méthode d'évaluation, appelée évaluation externe, est une des méthodes les plus robustes afin de déterminer la performance prédictive des

modèles (27). Cette dernière est basée sur l'erreur de prédiction (PE), décrite par l'équation suivante :

$$PE\ (\%) = \frac{C_{pred,i} - C_{obs,i}}{C_{obs,i}} \times 100\%$$

où C_{pred} et C_{obs} correspondent à la $i^{ème}$ concentration prédite par le modèle et la concentration respective observée, respectivement. De plus, afin de quantifier le biais et l'imprécision, la valeur médiane de l'erreur de prédiction (MDPE) et la valeur médiane absolue de l'erreur prédiction (MADPE) ont été estimées avec les équations suivantes :

Biais : $MDPE_i(\%) = median\ (PE_{ij}, j = 1, \dots, N_i)$

Imprécision: $MADPE_i(\%) = median\ (|PE_{ij}|, j = 1, \dots, N_i)$

CHAPITRE 2 – VISION DU PROJET

Ce projet de recherche regroupe plusieurs objectifs répartis sur trois différents volets :

- D'abord, le premier volet consiste à décrire les pratiques actuelles des posologies et de suivi thérapeutique des aminosides chez les patients aux soins intensifs dans les établissements du Québec.
- Ensuite, le deuxième volet représente une revue de la littérature des modèles PopPK d'aminosides développés pour les patients aux soins intensifs.
- Finalement, le troisième volet consiste à évaluer la performance prédictive des modèles trouvés au volet 2 à l'aide de deux populations adultes hospitalisées aux soins intensifs du Québec.

CHAPITRE 3 – MÉTHODOLOGIE

Volet 1 – Questionnaire sur les pratiques posologiques des aminosides aux soins intensifs

Méthodologie

Afin de décrire l'ensemble des pratiques actuelles des posologies et de suivi thérapeutique des aminosides auprès des patients aux soins intensifs dans les établissements du Québec, un questionnaire a été développé et distribué à travers la province. Ce questionnaire a été conçu sur la plateforme Microsoft Forms® (édition Microsoft 365) et comprenait des questions à choix de réponses et à court développement afin de minimiser le temps de réponse. Le questionnaire contenait les cinq sections suivantes : Informations générales sur l'établissement de santé, l'usage des régimes posologiques, l'adaptation posologique à partir de la fonction rénale, les cibles ainsi que les outils utilisés lors du suivi thérapeutique. La qualité et la pertinence des questions et réponses ont été vérifiées par un pharmacien de clinique, expert en antibiogouvernance. Ce questionnaire visait ainsi le ou la pharmacien(ne) responsable de l'antibiothérapie de l'institution en question. La distribution de ce questionnaire a été effectuée par courriel entre les mois de Mai et Juin 2020. Les réponses ont été collectées automatiquement, de façon anonyme, sur la plateforme Microsoft Forms® et les résultats ont été analysés de façon descriptive à l'aide du logiciel Microsoft Excel® (édition Microsoft 365).

Volet 2 – Revue de la littérature des modèles PopPK des aminosides aux soins intensifs

Méthodologie

Ce deuxième volet du projet consiste à décrire la pharmacocinétique des aminosides auprès des patients aux soins intensifs en résumant l'ensemble des modèles PopPK développés et publiés concernant l'amikacine, la gentamicine et la tobramycine. Pour se faire, une revue de la littérature a été effectuée sur Medline/Pubmed en utilisant, entres-autres, les différents termes suivants : 'amikacin', 'gentamicin', 'tobramycin', 'pharmacokinetic(s)', 'nonlinear mixed effect', 'population', 'intensive care' et 'critically ill'. La revue de la littérature a été complétée par deux

auteurs et une contre-vérification a également été effectuée. Quatre critères d'inclusion ont également été tenus en compte : l'article devait décrire un modèle PopPK, une administration intraveineuse d'amikacine, de gentamicine ou de tobramycine était nécessaire, la population à l'étude consistait à une population de patients adultes hospitalisés aux soins intensifs et l'article devait être publié en anglais. De plus, certains articles ont été exclus en fonction des critères suivants : le modèle a été conceptualisé à partir d'une approche non-compartimentale, la population à l'étude comprenait seulement des patients diagnostiqués pour la fibrose kystique étant donné les différentes caractéristiques physiopathologiques comparativement aux patients des soins intensifs pouvant influencer les paramètres PK des aminosides, si les articles étaient des revues et si les articles concernant l'amikacine ont été publiés avant 2015. En effet, cette présente revue permettait également la mise à jour de la revue par Marsot et al. (28) de tous les modèles PopPK d'amikacine développés jusqu'en 2015.

À partir des modèles retenus, plusieurs informations ont été récoltées, entre autres, les caractéristiques démographiques de la population à l'étude, le design de l'étude, les régimes posologiques utilisés, les informations sur la collecte de dosages sanguins, les méthodes de modélisation PopPK, les formules des modèles structuraux et statistiques et les méthodes utilisées pour évaluer les modèles.

Volet 3 - Évaluation externe des modèles PopPK

Méthodologie

Données-patients

Les dossiers médicaux des patients adultes admis aux soins intensifs à l'Hôpital Sacré-Cœur de Montréal (HSCM) entre 2009 et 2019 ou de l'Institut Universitaire de Cardiologie et Pneumologie de Québec (IUCPQ) entre 2014 et 2020 et ayant reçu au moins une dose d'amikacine, de gentamicine ou de tobramycine et ayant au moins un dosage de concentration ont été analysés de façon rétrospective.

Plusieurs données ont été collectées dont les informations démographiques, les doses d'aminosides administrés, les valeurs de dosages d'aminosides, les temps et dates de toutes les administrations et dosages sériques, les médicaments concomitants et l'historique médical.

Modèles évalués

Les modèles PopPK retenus lors de la revue de la littérature (volet 2) et ayant été développés avec NONMEM® ont été évalués avec les bases de données-patients obtenus à l'HSCM et l'IUCPQ. Pour chaque modèle, trois évaluations ont été effectuées : la première avec la population de l'HSCM seulement, la deuxième avec la population de l'IUCPQ seulement et la troisième avec l'ensemble des deux populations québécoises.

Évaluation externe de la performance prédictive des modèles PopPK

L'évaluation externe a été effectuée à l'aide du logiciel NONMEM® (version 7.5: ICON Development Solutions), tandis que les graphiques ont été développés sur R (version 4.0.3). La performance prédictive des modèles s'est basée sur l'erreur de prédiction (PE), décrite par l'équation suivante :

$$PE\ (\%) = \frac{C_{pred,i} - C_{obs,i}}{C_{obs,i}} \times 100\%$$

où C_{pred} et C_{obs} correspondent à la $i^{ème}$ concentration prédite par le modèle et la concentration respective observée, respectivement. De plus, afin de quantifier le biais et l'imprécision, la valeur médiane de l'erreur de prédiction (MDPE) et la valeur médiane absolue de l'erreur prédiction (MADPE) ont été estimées avec les équations suivantes :

Biais : $MDPE_i(\%) = median\ (PE_{ij}, j = 1, \dots, N_i)$

Imprécision: $MADPE_i(\%) = median\ (|PE_{ij}|, j = 1, \dots, N_i)$

Ces marqueurs permettent de déterminer si le modèle prédit adéquatement les concentrations observées en clinique. Une sous- ou sur-prédiction des concentrations peut engendrer l'administration de futures doses considérées non-optimales pour le patient. Dans le but d'être considéré non-biaisés, la valeur de MDPE devrait se situer entre -20 et 20%, tandis qu'afin d'être considéré précis, la MADPE devrait être ≤ 30% (29, 30). Ces limites sont généralement émises lors de l'évaluation de la performance prédictive de plusieurs modèles popPK d'antiinfectieux auprès de populations spéciales (31 - 34).

Finalement, des simulations appelées *normalized prediction distribution error* (NPDE) permettent d'établir de façon globale si le modèle PopPK est adéquat avec les bases de données indépendantes.

En fonction de la disponibilité des données-patients obtenues à l'HSCM et l'IUCPQ, l'évaluation des modèles d'amikacine, de gentamicine et de tobramycine sera effectuée.

CHAPITRE 4 – RÉSULTATS

Article #1: AMINOGYLCOSIDES' DOSING AND MONITORING PRACTICES IN CRITICALLY ILL PATIENTS IN QUEBEC HOSPITALS

Alexandre Duong[1,2], Daniel J. G. Thirion[1,3], David Williamson[1,4], Chantale Simard[5,6], Amélie Marsot[1,2,7]

[1] Faculté de Pharmacie, Université de Montréal, Montréal, Canada; [2] Laboratoire de Suivi Thérapeutique Pharmacologique et Pharmacocinétique, Faculté de Pharmacie, Université de Montréal, Montréal, Canada; [3] Centre Universitaire de Santé McGill, Université McGill, Montréal, Canada; [4] Hôpital Sacré-Cœur de Montréal, Université de Montréal, Montréal, Canada; [5] Institut Universitaire de Cardiologie et Pneumologie de Québec, Québec, Canada; [6] Faculté de Pharmacie, Université de Laval, Québec, Canada; [7] Centre de Recherche, CHU Sainte Justine, Montréal, Canada

Nature de la contribution pour cet article : Conceptualisation, méthodologie (création et distribution du questionnaire et collecte de données), analyse des résultats, rédaction et finalisation

Statut de l'article: Soumission au *International Journal of Chemotherapy*

Abstract

Contexte Les aminosides sont reconnus pour leur index thérapeutique étroit, nécessitant ainsi une individualisation au niveau des régimes posologiques et du suivi thérapeutique pour les populations spéciales ayant une pharmacocinétique altérée, telles que les personnes âgées et les patients aux soins intensifs. En fonction des particularités des aminosides au niveau de leur efficacité et toxicité, plusieurs régimes posologiques et nomogrammes ont été développés au cours des dernières décennies. L'objectif de cet article est de décrire les pratiques habituelles de posologies et de suivi thérapeutique posologique de l'amikacine, la gentamicine et la tobramycine au sein des patients hospitalisés en unités de soins intensifs dans les établissements de santé à travers la province du Québec. **Méthodologie** Ce questionnaire a été développé avec des questions à choix multiples et à court développement sur la plateforme Microsoft Forms®. Les questions et réponses ont été révisées par un pharmacien de clinique expert en maladies infectieuses. Ce questionnaire visait le pharmacien responsable de l'antibiothérapie de chaque établissement. Les réponses ont été collectées jusqu'à 8 semaines suivant la première distribution et ont été analysées de façon descriptive. **Résultats** Ce questionnaire a eu un taux de réponse de 64.7% à travers la province de Québec et représentant environ 60% du nombre de lits (42% de lits aux soins intensifs) pour une population de 8.4 millions personnes. Les régimes posologiques les plus utilisés de gentamicine et de tobramycine étaient de 5 à 7 mg/kg pour les doses uniquotidiennes (ODD), 1.7 mg/kg chaque 8 heures et 2.5 mg/kg chaque 12 heures pour les doses fractionnées (MDD). Les cibles thérapeutiques pour les concentrations pré-doses étaient similaires pour la gentamicine et la tobramycine avec des valeurs de 0.5 à 1 mg/L pour les régimes d'ODD et MDD. Tandis que les concentrations maximales étaient de 15 à 25 mg/L et 3 à 10 mg/L pour les régimes d'ODD et MDD, respectivement. L'adaptation posologique était principalement basée sur le jugement clinique du clinicien ou à l'aide d'un outil de calcul. L'amikacine n'était pas fréquemment administrée chez les patients aux soins intensifs dans les établissements du Québec. Ainsi, les habitudes de dosage et de suivi thérapeutique n'ont pas été adéquatement définies. **Conclusions** Les habitudes de posologies tendent de plus en plus vers une approche ODD à travers les décennies au Québec. Les cibles thérapeutiques étaient majoritairement alignées avec la littérature. En sachant la variabilité observée à travers les établissements du Québec et l'intérêt grandissant de l'adaptation posologique basée sur la modélisation bayésienne, une standardisation et une optimisation des suivis thérapeutiques posologiques pourraient être considérées.

1. Introduction

Aminoglycosides are a broad-spectrum class of antibiotics used for the treatment of life-threatening infections, especially for suspected Gram-negative bacteria, such as the *Enterobacteriaceae and Pseudomonas sp.* For maximum efficacy, aminoglycosides should be dosed to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets of peak concentration over minimal inhibitory concentration (C_{max}/MIC) of 8 to 10. Aminoglycosides' nephrotoxicity rates are 10 to 20% and 0% to 14% for multiple-daily doses (MDD) and once-daily dose (ODD), respectively, whereas ototoxicity in patients causing hearing deficits ranges between 2% and 25% (1, 2). Therefore, due to the possibility of toxicity and high inter- and intra-variability in aminoglycosides' response, various dosing and therapeutic drug monitoring (TDM) methods have been developed throughout the years (3). TDM is even more prioritized in critically ill patients especially considering the potential toxicity caused by aminoglycosides administration and the high mortality rates ranging from 27 to 38% for severe infections caused by Gram-negative bacteremia (4, 5). In fact, critically ill patients often present pathophysiological modifications, such as nephrotoxicity, that could lead to an altered antimicrobial pharmacokinetic profile and consequently, inadequate drug exposure (6). Over the years, with the growing interest of dose personalization and optimisation, multiple aminoglycosides population pharmacokinetics (Pop-PK) models have been developed in order to better understand the challenges of aminoglycosides dosing and TDM in critically ill patients (7, 8).

Traditionally, patients are administered MDD of aminoglycosides. However, multiple meta-analyses have associated ODD with reduced nephrotoxicity and similar efficacy as compared to traditional dosing (3, 9). Although, the use of ODD has been demonstrated in several populations (10-13), its application and effectiveness in critically ill patients remains unclear (14-17). Also, legislation and required organisational practices remain unclear regarding TDM, therefore practices may vary between institutions. The purpose of this study is to investigate aminoglycoside dosing and monitoring practices in Quebec hospitals. This survey also aims to compare the results with practices within other jurisdictions according to international guidelines to inform required practice changes and opportunities for intervention.

Novelty of the Work: The present survey pertains to standard practices in terms of current dosing and monitoring practices of aminoglycosides specifically in the critically ill patients in the

province of Quebec. As the previous Canadian and American surveys describing practices were completed 20 years ago, the results may also reflect practices in a national level. Moreover, the results from this study shed light on the need of optimizing and standardizing clinical care in this frail population.

2. Methods

2.1 Questionnaire and target population.

An initial version of the survey was designed with Microsoft Forms® and drafted by a master's student and a professor from Université de Montréal from the team *Laboratoire Suivi Thérapeutique Pharmacologique et Pharmacocinétique*. This survey is designed to describe aminoglycoside dosing and monitoring practices specifically in critically ill patients across the province of Quebec. For this purpose, the survey includes mostly multiple-choice and short answers questions to maximizing response rate through an optimal survey completion time.

This survey includes five sub-sections aimed at describing the protocol and practices in each institution. Section I included general information on the institution. For sections II to V, information on the dosing regimens and usage, drug adaptation depending on renal function, therapeutic drug monitoring (targets and practices) and tools used for therapeutic drug monitoring were obtained from questions based on the following hypothetical situation: "A typical patient's (BMI between 18.5 and 25.5 kg/m^2 and a creatinine clearance (CrCl) between 60 and 120 mL/min) is diagnosed with a serious Gram-negative infection leading to sepsis". This hypothetical case was chosen in regards that it would reflect the most common standards of practice of aminoglycosides therapeutic drug monitoring.

The initial version of the survey underwent validation by a clinical pharmacist, expert in infectious diseases and TDM, in order to assess the relevancy and accuracy of questions and multiple choices answers.

2.2 Survey distribution.

This survey was sent, by e-mail between May 2020 and June 2020 inclusively, to the lead pharmacist responsible for antimicrobial stewardship in each hospital established in the province of Quebec. A first email was sent to each head of pharmacy department of every Integrated Health

and Social Services Centres (CISSS) and Integrated University Health and Social Services Centres (CIUSSS) and other institutions that are not affiliated with any CISSS or CIUSSS. This first communication allowed the presentation of the project to every lead pharmacist responsible for antimicrobial stewardship in each hospital from the CISSS or CIUSSS. This communication also allowed the presentation of the project, the informed consent form, and the hyperlink to the electronic survey. Reminder emails were sent twice, 4 and 8 weeks following the first email.

2.3 Data analysis.

Following two weeks of data collection, the responses were automatically and anonymously collected with *Microsoft Forms*®. Frequencies and descriptive statistics were reported using number of observations, mean and standard deviation.

3. Results

The response rate was 64.7%, where out of the 51 surveys sent by email, a total of 33 responses were recorded over 8 weeks for this survey of standard practices. It's important to note that four head of pharmacy department of CISSS/CIUSSS, also working as clinical pharmacists, responded to the study on behalf of all institutions in their respective CISSS/CIUSSS, corresponding to a total of 28 institutions.

Summary on the institution characteristics is presented in Table 1, while Table 2 lists the number of responders for each region and the corresponding approximate number of beds represented. The number of hospital beds in this survey represents approximately 60% of the total hospital beds (42% of total ICU hospital beds) across the province of Quebec for a population of 8.4 million people (18).

Table 1: Summary characteristics of Quebec institutions participating in this study

Characteristics	**Response by count (% out of number of respondents) (n=33)**
University affiliated	
Yes	15 (45)
No	18 (55)
Institution with an ICU	
Yes	29 (88)
No	4 (12)
Population treated:	
Adult	16 (48)
Pediatrics	1 (4)
Adults and Pediatrics	16 (48)

ICU: Intensive Care Unit

Table 2: Number of respondents per region and approximate number of total and ICU hospital beds represented

Regions	**Respondents (n=33)**	**Approximative number of total (ICU) hospital beds represented**
Bas-Saint-Laurent	1*	490 (28)
Saguenay-Lac-Saint-Jean	3	423 (30)
Capitale-Nationale	1*	2138 (125)
Chaudières-Appalaches	3	452 (36)
Mauricie-et-du-Centre-du-Québec	3	400 (22)
Estrie	0	0 (0)
Montreal	8	2567 (142)
Outaouais	3	480 (24)
Gaspésie-Îles-de-la-Madeleine	1*	228 (23)
Abitibi-Témicasmingue	0	0 (0)
Laval	1*	473 (22)
Laurentides	4	379 (16)
Lanaudière	0	0 (0)
Montérégie	4	942 (44)
Total	33	8972 (512)

*Respondents answered on behalf of all institutions in their respective region.

Table 3 presents the different responses for amikacin and gentamicin/tobramycin ODD regimens. Based on these results, ODD regimens most used in Quebec hospitals ranged from 5-7 mg/kg for gentamicin and tobramycin, whereas amikacin is usually not administered (NA) since only 7 institutions are using this aminoglycoside. However, a 15 mg/kg would be given as per standard practices.

As for multiple-daily dose (MDD) in Table 4, the dose most used for gentamicin and tobramycin was 1.7 mg/kg every 8 hours, whereas amikacin is usually administered at 5 mg/kg every 8 hours or 7.5 mg/kg every 12 hours.

For both tables, when the answer "other" was selected, respondents had the opportunity to specify in short sentences their answer. When compiling these results, the written answers were similar to the presented multiple choices but with added specifications and details in their standard practices. When calculating the dose required, 79% of respondents answered that they are using patient's actual bodyweight.

Table 3: Once-daily dose regimens for Amikacin, Gentamicin and Tobramycin

	Amikacin Once-daily dose, mg/kg (n=33)				Gentamicin/Tobramycin Once-daily dose, mg/kg (n=33)				
	15	Other	NA	Ø ODD	5	7	Other	NA	Ø ODD
% of respondents (No./ Total No.)	9.1 (3/33)	12.1 (4/33)	78.8 (26/33)	-	57.6 (19/33)	12.1 (4/33)	6.1 (2/33)	18.1 (6/33)	6.1 (2/33)

Note: Multiple choices with zero response were not presented: 20, 25 and 30 mg/kg for Amikacin and 2.5 and 3 mg/kg for gentamicin and tobramycin. NA: Not administered, ODD: Once-daily-dosing. Ø ODD: ODD not used

Table 4: Multiple-daily dose regimens for Amikacin, Gentamicin and Tobramycin

	Amikacin Multiple-daily dose, mg/kg (n=7)				Gentamicin/Tobramycin Multiple-daily dose, mg/kg (n=27)				
	5 Q8h	7.5 Q12h	Other	Ø MDD	1 Q8h	1.7 Q8h	2.5 Q12h	Other	Ø MDD
% of respondents (No./ Total No.)	14.2 (1/7)	42.9 (3/7)	42.9 (3/7)	-	3.7 (1/27)	51.9 (14/27)	7.4 (2/27)	14.8 (4/27)	22.2 (6/27)

Note: Respondents who answered that the aminoglycoside(s) was/were not administered in their establishment were removed from this table. Ø MDD: MDD not used. Q8: every 8 hours, Q12: every 12 hours

Table 5 presents monitoring schedules and therapeutic targets for gentamicin and tobramycin. Considering around 80% of institutions do not use amikacin, the corresponding results were not presented. In terms of the frequency of TDM, most institutions responded monitoring samples twice weekly or as per clinical judgment. The latter was defined by the patient's condition or renal function. During ODD, 72% of the respondents reported that the first monitoring sample is taken on the 2nd or 3rd dose, while during MDD, the first monitoring sample is reported to be taken on the 3rd or 4th dose by 94% of the respondents. Both peak and trough targets are used by the majority of the participants, whereas two institutions only use target trough levels. Trough target for gentamicin and tobramycin tends to be less than or around the limit of detection (0.3-0.5 mg/L) to 1 mg/L for both types of dosing administration. Whereas for peak targets, most clinicians are aiming values between 15 and 25 mg/L for ODD. For MDD, 64% of the peak targets were manually entered by the respondents, with 12 of them answering that values targeted were between 8 and 10 mg/L or lower depending on the indications, while the other 9 respondents mentioned intervals with the upper bound being close to 8 mg/L.

As per Table 6, when asked on the different methods used if the therapeutic targets were not reached, most clinicians answered that they rely on clinical judgment (33%) or a calculation tool (27%) such as *ClinCalc, Vigiliance,* a homemade calculation file, software from *Centre Hospitalier Universitaire Ste-Justine* and *GlobalRPH* for dose adaptation. Other answers selected were the usage of a non-compartmental approach, a compartmental approach, a nomogram or they did not know.

Table 5: Monitoring schedules and therapeutic targets of serum aminoglycosides for Gentamicin and Tobramycin administered with ODD and MDD

Variables	No. (%) of respondents	
Frequency		
On administration day	2 (6)	
Once weekly	6 (19)	
Twice weekly	12 (36)	
Thrice weekly	1 (3)	
Per clinical judgment	12 (36)	
	ODD	**MDD**
1st monitoring sample on the…		
…1st dose;	6 (19)	-
…2nd dose;	13 (41)	-
…3rd dose;	10 (31)	17 (55)
…4th dose;	3 (9)	12 (39)
…5th dose;	-	2 (6)
Targets		
Trough (mg/L)		
≤ 0.3	5 (15)	-
≤ 0.5	12 (37)	4 (12)
≤ 1	10 (30)	25 (76)
NA	6 (18)	4 (12)
Peak (mg/L)		
3-8	-	9 (27)
8-10	-	12 (37)*
15-25	17 (52)	4 (12)
26-35	2 (6)	1 (3)
NA	14 (42)	7 (21)

ODD: Once-daily dosing, MDD: Multiple-daily dosing, NA: Not Applicable

*Amongst them, 5 respondents mentioned that they would also wider ranges from 3 to 8 mg/L depending on the indication

Table 6: Methods of dose adaptation when therapeutic targets are not reached

Methods	No. (%) of respondents
Frequency	
Per clinical judgment	11 (33)
Non-compartmental approach	3 (9)
Compartmental approach	6 (18)
Usage of calculation tool	9 (27)
Usage of a nomogram	2(6)
Don't know	2 (9)

4. Discussion

Our survey had a response rate of 64.7%. Considering that the respondents were from several regions across the province and that the responses from this survey cover more than half of the total hospital beds available for the population of Quebec, this response rate was deemed adequate to illustrate the dosing and monitoring practices of aminoglycosides in critically ill patients.

4.1 Dose administration

Since the appearance of multiple recommendations in favor of ODD for aminoglycosides in the early 2000s (10-13), it appears that institutions have been leaning towards this practice. In fact, back in 1999 Gin et al. surveyed 134 Canadian hospitals on their frequency of administrating aminoglycosides with a once-daily dosing regimen (19). About 40% of these hospitals answered that the use of ODD was infrequent. In the present study across Quebec hospitals, 6% did not administer aminoglycosides with an ODD. In comparison to MDD, where 22% of the clinicians reported not using this dosing regimen in critically ill patients.

In fact, clinicians in their respective institution mentioned that they preferred ODD over MDD, thereby suggesting similar dosing practices according to best evidence (10-13). Furthermore, for both gentamicin and tobramycin, the most common dosing regimens answered were generally similar to the simulated dosing regimens from their respective aminoglycosides Pop-PK models in critically ill patients (8). A nationwide survey on aminoglycosides ODD was also performed in the United States by Chuck et al. in 1998 (20). The latter showed that aminoglycosides ODD was used in 74.7% of the institutions with daily regimens trending towards 5 mg/kg and higher. Chuck et al.

suggested that the disparity of ODD usage may be due to sampling methods, the interpretation of ODD usage itself or non-response bias based on the response rates.

In comparison with Canada, gentamicin and tobramycin ODD remained similar to the previous survey where the latter retrieved an average dose of 5.6 (±0.8) mg/kg/day whereas this present study pointed out that close to 70% of clinicians are using 5 to 7 mg/kg per day (19). These results are also in-line with the european dosing recommendations for gentamicin and tobramycin, respectively with values of 3 to 6 mg/kg per day and 3 to 5 mg/kg per day for adult patients with normal renal function (21, 22). Furthermore, australian guidelines also recommends administrating 4 to 7 mg/kg of Gentamicin ODD for non- and critically ill patients (23), whereas most United States guidelines recommends 5 to 7 mg/kg of Gentamicin per day depending on the situation (24).

The most common dosing regimen given multiple times daily (1.7 mg/kg every 8 hours) would result in a similar total daily dose as per ODD. Although it seems that there was a gradual shift in aminoglycosides dosing administration, from MDD to ODD, over the years, the frequency of sample monitoring remains similar across the years: 2 times weekly and as per clinical judgment were the most frequent answer for both surveys. Despite the frequency of monitoring samples remaining similar, the monitoring of trough serum concentrations only was more frequent (61%) across Canadian hospitals in 1999, as compared to only 7% of Quebec institutions nowadays. In the Gin et al. survey, the 5 most common aminoglycosides indications reported were urinary tract infections, intra-abdominal infections, pneumonias, sepsis, and bacteremia.

4.2 Therapeutic targets

Overall, only 28% reported using both peak and trough targets for monitoring aminoglycosides concentrations (19). In similar fashion in the American survey, only 30% of the institutions reported using peak and trough concentrations, specifically for ODD administration (20). As for amikacin administration, Quebec hospitals are not likely to using this aminoglycoside in these types of situations. Moreover, the 1999 Canadian survey also did not include this drug in their study (19), whereas the 1998 American survey showed that 72% of the institutions were administrating amikacin daily dose between 10 and 15 mg/kg for adult patients (20). As of now, no other surveys on actual aminoglycoside dosing and monitoring practices have been performed in general hospitalized patients nor in ICU patients. Therefore, comparison of these results with other

countries may only be feasible with aminoglycosides product's monographs from their respective countries.

Generally, peak therapeutic targets of C_{max}/MIC ratio ≥ 8-10 have been suggested in multiple studies as an endpoint providing both optimal efficacy while also preventing antimicrobial resistance (1, 24-26), with MIC breakpoints based on the United States Committee on Antimicrobial Susceptibility Testing (USCAST) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Recently, these targets were also frequently considered as a PK/PD target in the development of several population-pharmacokinetics (Pop-PK) models across the United States and Europe (8). Gentamicin and tobramycin peak targets appeared to be respected for ODD and MDD for most of Quebec institutions considering, for example, a MIC value of 1 to 2 µg/mL for *Staphylococcus spp, Pseudomonas spp and Enterococcus spp.* as per USCAST and EUCAST (27, 28). However, considering the latter MIC values, three respondents mentioned using peak targets higher than needed.

As for the toxicity targets, trough targets were suggested to be lower than 0.5 to 2 mg/L for all three aminoglycosides. These predose recommendations were adequately followed based on all the survey's responses, therefore indicating that Quebec institutions' standard practices are in line with the literature (1, 24-26).

In addition to peak and trough targets, the australian agency also recommends estimating the cumulative area under the curve for the first 24 hours (AUC_{0-24}) for gentamicin and tobramycin with values between 70 to 100 mg*h/L. Panel Members nominated by European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/Pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and International Society of Antimicrobial Chemotherapy (ISAC) also recommended AUC_{0-24}/MIC between 80-100 for all three aminoglycosides for critically ill patients (26). However, the latter often needs to be calculated using bayesian softwares in order to better achieve target exposure as early as possible in the drug therapy. Although those bayesian programs seemed to be used in australian institutions (29), these software were not used in Quebec hospitals.

4.3 Dose adaptation

In fact, when faced with peak or trough concentrations not in the therapeutic range, one third of respondents answered that their dose adaptation was based on clinical judgment or with the help of a software. When softwares are to be used, the most common were *Vigilance*© (n=16), software from *Centre Hospitalier Universitaire Sainte-Justine* (n=11), the institution's own software (n=10), *ClinCalc*© (n=5) and *Global RPH*© (n=5). Generally, dose optimisation based on mono-compartmental approach may lead to under- or overestimation and depends on steady-state concentrations, therefore leading to delayed establishment of optimal antimicrobial therapy, whereas non-compartmental approach is not a method for dose adaptation. Moreover, only two institutions mentioned the Hartford and Urban-Craig dosing nomograms. (30, 31). The Hartford nomogram was developed based on a population with characteristics that may highly influence aminoglycosides pharmacokinetics, for example: pediatric, pregnant, dialysis patients and critically ill patients. Because most nomograms are to be used in patients with normal renal function may explain why they are not used in the ICUs in Quebec. The nomogram also implemented additional recommendations for ODD to lengthen the dosing interval to 36 and 48 hours for lower CrCl values of 40 to 59 ml/min and 20 to 39 ml/min, respectively. When CrCl values are lower than 20 ml/min, dosing interval should be handled case-by-case and MDD should be considered. It is to note that appropriateness of the Hartford nomogram in critically ill patients has showed that its application may not be suited to manage efficacy and toxicity (32-34).

Several limitations of this survey should be acknowledged. Firstly, answers provided in any type of surveys are prone to be subjective from the respondents and are difficult to be validated. Moreover, the distribution of the survey to clinicians during COVID-19 could have been one of the principal reasons explaining our somewhat limited response rate. Results from this survey should be generalizable to other institutions within the province of Quebec, considering the various responses from rural and urban regions. However, since only Quebec institutions were targeted in this survey, extrapolation of these results to other jurisdictions should be done cautiously.

5. Conclusion

This present survey aimed to describe the dosing and monitoring practices of aminoglycosides in critically ill patients in Quebec's institutions. For gentamicin and tobramycin, trough targets used were consistent in Quebec institutions and are adequate based on evidence from literature. For peak

targets, responses provided showed that target intervals were wider than as per recommended in the literature. Moreover, the usage of actual body weight in clinical settings may not always be appropriate, especially when dealing with obese patients. Interpretation of amikacin monitoring is not reliable considering the low usage of amikacin in Quebec institutions. When therapeutic targets are not initially reached, most common methods of dose adaptation were split between clinical judgment and with the help of a home software. Considering the varying methods used for therapeutic drug monitoring, standardization of the latter should be prioritized across Quebec's institutions. Therefore, any improvement initiatives or updates regarding monitoring practices should be based on critical review of the literature and its application in clinical settings. Moreover, the increasing interest from clinicians on model-informed precision dosing for antimicrobials with narrow therapeutic index may lead to optimization of aminoglycosides usage in the near future.

6. References

1. Moore RD, Lietman PS, Smith CR. Clinical Response to Aminoglycoside Therapy: Importance of the Ratio of Peak Concentration to Minimal Inhibitory Concentration. The Journal of Infectious Diseases. 1987;155(1):93-9.
2. Ariano RE, Zelenitsky SA, Kassum DA. Aminoglycoside-induced vestibular injury: maintaining a sense of balance. Ann Pharmacother. 2008;42(9):1282-9.
3. Stankowicz MS, Ibrahim J, Brown DL. Once-daily aminoglycoside dosing: An update on current literature. American Journal of Health-System Pharmacy. 2015;72(16):1357-64.
4. Kang C-I, Kim S-H, Park WB, Lee K-D, Kim H-B, Kim E-C, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrobial agents and chemotherapy. 2005;49(2):760-6.
5. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Septic Acute Kidney Injury in Critically Ill Patients: Clinical Characteristics and Outcomes. Clinical Journal of the American Society of Nephrology. 2007;2(3):431.
6. Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Medicine. 2013;39(12):2070-82.
7. Marsot A, Guilhaumou R, Riff C, Blin O. Amikacin in Critically Ill Patients: A Review of Population Pharmacokinetic Studies. Clinical Pharmacokinetics. 2017;56(2):127-38.
8. Duong A, Simard C, Wang YL, Williamson D, Marsot A. Aminoglycosides in the Intensive Care Unit: What Is New in Population PK Modeling? Antibiotics. 2021;10(5).
9. Barclay ML, Kirkpatrick CMJ, Begg EJ. Once Daily Aminoglycoside Therapy. Clinical Pharmacokinetics. 1999;36(2):89-98.
10. Rozdzinski E, Kern WV, Reichle A, Moritze T, Schmeiser T, Gaus W, et al. Once-daily versus thrice-daily dosing of netilmicin in combination with β-lactam antibiotics as empirical therapy for febrile neutropenic patients. Journal of Antimicrobial Chemotherapy. 1993;31(4):585-9.
11. Smyth A, Tan KHV, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomised controlled trial. The Lancet. 2005;365(9459):573-8.
12. Stabler SN, Ensom MHH. Extended-interval aminoglycoside therapy for adult patients with febrile neutropenia: a systematic review. Can J Hosp Pharm. 2011;64(3):182-91.
13. Whitehead A, Conway SP, Etherington C, Caldwell NA, Setchfield N, Bogle S. Once-daily tobramycin in the treatment of adult patients with cystic fibrosis. European Respiratory Journal. 2002;19(2):303.
14. Rea RS, Capitano B, Bies R, Bigos KL, Smith R, Lee H. Suboptimal Aminoglycoside Dosing in Critically Ill Patients. Therapeutic Drug Monitoring. 2008;30(6).
15. Barletta JF, Johnson SB, Nix DE, Nix LC, Erstad, Brian L. Population Pharmacokinetics of Aminoglycosides in Critically Ill Trauma Patients on Once-Daily Regimens. Journal of Trauma and Acute Care Surgery. 2000;49(5).
16. Roger C, Louart B, Elotmani L, Barton G, Escobar L, Koulenti D, et al. An international survey on aminoglycoside practices in critically ill patients: the AMINO III study. Annals of Intensive Care. 2021;11(1):49.
17. Roger C, Nucci B, Louart B, Friggeri A, Knani H, Evrard A, et al. Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis. Journal of Antimicrobial Chemotherapy. 2016;71(1):208-12.

18. Québec Gd. Établissements - soins intensifs adultes au Québec. In: Sociaux MdSedS, editor. 2020. p. 12.
19. Alfred S.Gin RA, Sheryl Zelenitsky, Murray Ducharme, Keith A.Rodvold, George A.Zhanel. The practice of once-daily aminoglycoside dosing in Canada: A national survey. Can J Hosp Pharm. 1999;52:12-7.
20. Chuck SK, Raber SR, Rodvold KA, Areff D. National Survey of Extended-Interval Aminoglycoside Dosing. Clinical Infectious Diseases. 2000;30(3):433-9.
21. (EMC) EMC. Gentamicin 40mg/ml Injection 2021 [Available from: https://www.medicines.org.uk/emc/product/6531/smpc.
22. (EMC) EMC. Tobramycin 40mg/ml Injection 2021 [Available from: https://www.medicines.org.uk/emc/product/10194/smpc.
23. Australia GoS. Aminoglycosides: Recommendations for use, dosing and monitoring - Clinical Guideline. 2020.
24. Bland CMP, Manjunath P.;Lodise, Thomas P. Reappraisal of Contemporary Pharmacokinetic and Pharmacodynamic Principles for Informing Aminoglycoside Dosing. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019;39(7):794-.
25. Kashuba ADM, Nafziger AN, Drusano GL, Bertino JS. Optimizing Aminoglycoside Therapy for Nosocomial Pneumonia Caused by Gram-Negative Bacteria. Antimicrobial Agents and Chemotherapy. 1999;43(3):623.
26. Abdul-Aziz MH, Alffenaar J-WC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper(). Intensive care medicine. 2020;46(6):1127-53.
27. (USCAST) TUSCoAST. 2021 USCAST Interpretive Tables. 2021. p. 47.
28. (EUCAST) ECOAST. Clinical breakpoints - breakpoints and guidance 2021.
29. Queensland So. Aminoglycoside Dosing in Adults. April 2018.
30. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrobial agents and chemotherapy. 1995;39(3):650-5.
31. Urban AW, Craig WA. Daily dosage of aminoglycosides. Curr Clin Top Infect Dis. 1997;17:236-55.
32. Tobias P, DeMott J, Varughese C, Gurnani P. 649: APPLICATION OF THE HARTFORD NOMOGRAM IN CRITICALLY ILL PATIENTS: A PHARMACOKINETIC STUDY. Critical Care Medicine. 2019;47(1).
33. Xie F, Wang Y, Peng Y, Cheng Z, Li S. Pharmacokinetic/pharmacodynamic evaluation of tobramycin dosing in critically ill patients: the Hartford nomogram does not fit. J Antimicrob Chemother. 2021.
34. Lee J, Yoon S, Shin D, Han H, An H, Lee J, et al. Predictive performance of gentamicin dosing nomograms. Drug Des Devel Ther. 2014;8:1097-106.

Article #2: AMINOGLYCOSIDES IN THE INTENSIVE CARE UNIT: WHAT'S 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, Canada; [2] Laboratoire de Suivi Thérapeutique Pharmacologique et Pharmacocinétique, Faculté de Pharmacie, Université de Montréal, Montréal, Canada; [3] Faculté de Pharmacie, Université Laval, Québec, Canada; [4] Centre de Recherche, Institut universitaire de cardiologie et pneumologie de Québec, Québec, Canada; [5] Hôpital Sacré-Cœur de Montréal, Montréal, Québec, Canada; [6] Centre de Recherche, CHU Sainte Justine, Montréal, Canada

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La version intégrale de l'article, sous la mise en page du journal, est présentée suivant l'abstract en français.

Abstract

Contexte Malgré que les aminosides soient fréquemment utilisés comme traitement contre les infections de type Gram-négatif, les régimes posologiques optimaux restent incertains, surtout auprès des patients hospitalisés aux soins intensifs. En effet, cela serait causé par la grande variabilité inter et intra-individuelle de la pharmacocinétique des aminosides dans cette population. **Objectif** Cette revue vise à décrire la pharmacocinétique des aminosides dans les patients hospitalisés aux soins intensifs. Cela sera possible en résumant tous les modèles PopPK publiés pour l'amikacine, la gentamicine et la tobramycine. **Méthodologie** La revue de la littérature a été effectuée sur Medline/Pubmed en utilisant les termes suivants : 'amikacin', 'gentamicin', 'tobramycin', 'pharmacokinetic(s)', 'nonlinear mixed effect', 'population', 'intensive care' et 'critically ill'. **Résultats** Dix-neuf articles ont été retenues, où la pharmacocinétique de l'amikacine, la gentamicine et la tobramycine a été décrite dans six, onze et cinq modèles, respectivement. Les modèles à deux compartiments décriraient mieux la pharmacocinétique de l'amikacine et de la tobramcyine, tandis que les modèles à un compartiment décriraient mieux la pharmacocinétique de la gentamicine. Les covariables les plus souvent considérées comme significatives étaient la clairance rénale et le poids corporel. À travers les trois aminosides, les variabilités interindividuelles moyennes de la clairance et du volume de distribution étaient de 41.6% et 22.0%, respectivement. Un consensus n'a pas été établi au niveau du régime posologique optimal pour chaque aminoside. **Conclusion** Cette revue a décrit les modèles PopPK d'amikacine de 2015 jusqu'à aujourd'hui ainsi que les modèles de gentamicine et de tobramycine des dernières décennies. Malgré les défis de l'évaluation externe, cette dernière devrait davantage considérée durant le développement de modèles PopPK. De plus, des études additionnelles incluant de nouvelles covariables, des simulations de régimes posologiques et une évaluation externe seraient nécessaires afin de mieux comprendre la pharmacocinétique des aminosides auprès des patients hospitalisés aux soins intensifs.

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Review

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

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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_{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 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 ototoxicity, therapeutic drugmonitoring (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** 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 intravenous amikacin, gentamicin, or tobramycin; (3) the studied population consisted of ICUadult patients; (4) the article was published in the English language.

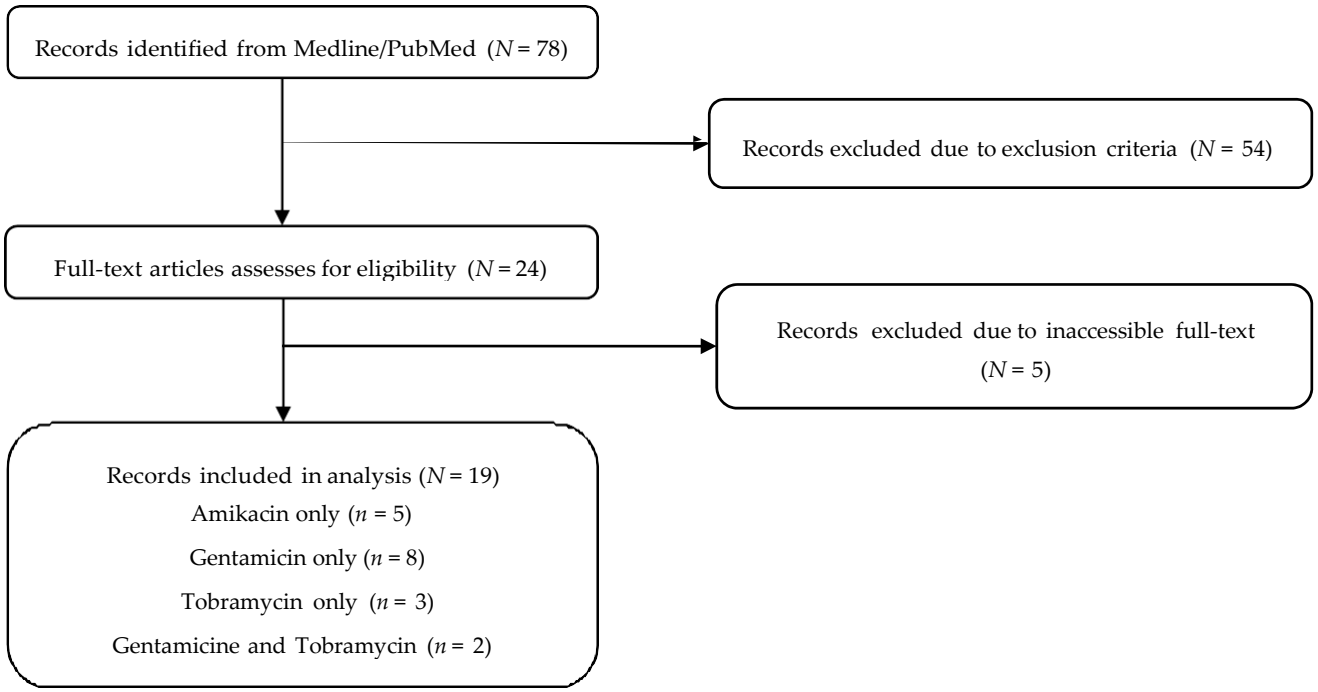

Figure 1. PRISMA chart.

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 8, 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, six 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	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 (h)
Amikacin	Boidin C [16]	2019	Retrospective (TDM)	Critically ill withsepsis	166 (108/58)	65 (19–85) [b]	76.5 [b] (41.5–137.5)	170 (137–190) [b]	25.6 (16–46) [b]	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] [b]	80 [73–89] [b]	167 [162–178] [b]	27 [24–32] [b]	15–30 mg/kg every 24 or 36 h	NR	9	261	(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] [b]	80 [65–94] [b]	NR	27 [25–32] [b]	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) [b]	170.1 ± 7.9	24.0 (16.0–38.2) [b]	Once daily IV dosing	1000 (500–1000)	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 (q24 h)	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	40.60 ± 42.67	NR	NR	NR
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 patientstreated for endocarditis due to Gram-positivemicro-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 was collected the next morning at 06:00 a.m., 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 the 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 q8 h or 80 to 240 mg/kg q12 or 24 h	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 h 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, and 10

Table 1. *Cont.*

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 (h)
	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 patien ts	65 (21/44)	69.3 (32–92)	76.2 (46-12 1)	173.9 (149-193)	NR	3 mg/kg q24 h	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 q12 h, q18 h, q24 h, q36 h, or q72 h	NR	2.8 ± 1.6	102	1 h 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
	Frenc h MA [21]	1981	Prospective and retros pective (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
	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 q24 h for 3–5 days	NR	NR	NR	Peak and trough
Tobramycin	Aarons L [33]	1989	Retrospective (TDM)	Unselected poplation of patients treated with tobramycin	97 (52/45)	50.6 ± 19.0 (51.0; 16–8 5) [c]	66.5 ± 12.5 (66.8; 42-120) [c]	NR	NR	NR	NR	(1–9)	322	2, 6 h after the dose for patients with normal renal function 2, 6, 12, and 24 h for patients with impaired renal function
	Hennig S [34]	2013	Retrospective (TDM)	Patients with or without cystic fibrosis	208 (109/99)	31.7 (18.0–8 5. 0)	58.0 (37.0–12 0. 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 the mean ± standard deviation (range) [interquartile range]. [b] Values are expressed as the median (range) [interquartile range]. [c] 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	Modeling			Simulation	
		Software	Model	Evaluation	Optimal Dosing Regimen	Target
Amikacin	Boidin C [16]	NPAG (Pmetrics)	2 compartments	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 an MIC of 8 mg/L	C_{max}/MIC ≥ 8, AUC_{0-24}/MIC ≥ 75 and C_{min} ≤ 2.5 mg/L
	Roger C [17]	NPAG (Pmetrics)	2 compartments	Advanced internal (bootstrap, n = 1000)	25 mg/kg every 48 h in critically ill patients receiving CRRT based on an MIC of 8 mg/L	C_{max}/MIC ≥ 8 and C_{min} ≤ 2.5 mg/L
	Carri é C [18]	Monolix	2 compartments	Advanced internal (NPDE)	25–30 mg/kg every 36–48 h based on an MIC of 8 mg/L	C_{max}/MIC ≥ 8, AUC_{0-24}/MIC ≥ 75 and C_{min} ≤ 2.5 mg/L
	Aréchiga-Alvarado 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 Cmax/MIC ≥ 8 was above 75% for creatinine clearance ranging from 60 mL/min to 200 mL/min [a]	C_{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	–	–
Gentamicin	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_{max} ≥ 8 mg/L $AUC_{min,48h}$ ≥ 140 $AUC_{max,48h}$ ≤ 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 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 ≥ 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_{max}/MIC ≥ 8
	Hodiamont CJ [26]	NONMEM 7.2	2 compartments	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 compartments	Advanced internal (bootstrap, n = 1000)	6 mg/kg every 48 h before the commencement of EDD-f	C_{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	Ext rnal 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	Modeling			Simulation	
		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_{max}/MIC > 10, C_{min} ≤ 1 mg/L AUC between 80 and 125 mg·h/L for MIC ≤ 1 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 mgQ12 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_{max} = 6 mg/L and average concentrations within a dosing interval ≤ 4 mg/L
	Hennig S [34]	NONMEM 7.2	2 compartments	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 concen tration– time curve; CLcr, creatinine clearance; C_{max}, maximum con centration; 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 represen tation of probability of target attainment based on differen t 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} 10 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.

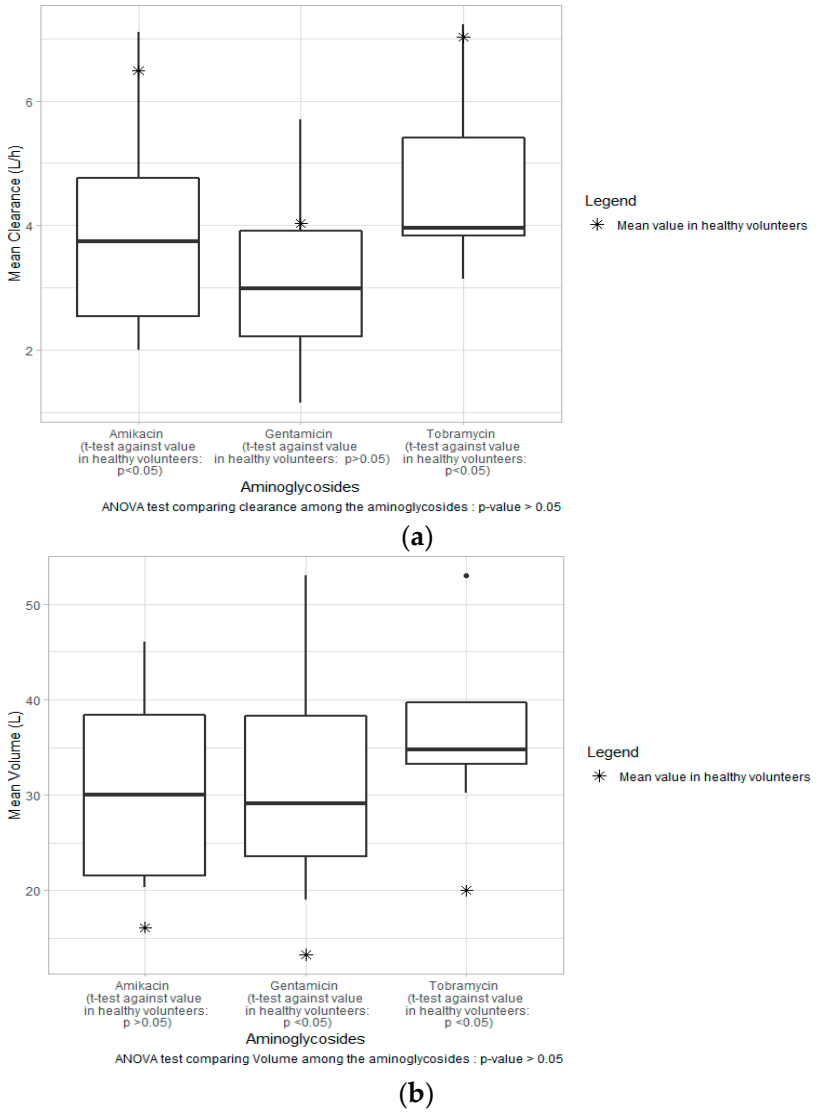

Figure 2. (**a**) Range of mean clearance across studies stratified by aminoglycosides (amikacin, gentamicin, and tobramycin) with mean clearanc e value in healthy volunteers (dotted line). (**b**) Range of mean vo lume of distribution across studies stratified by aminoglycosides (amikacin, gentamicin, 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 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 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 (3.8×10^{-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 µmol/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_{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}/MIC ≥ 8, AUC_{0-24}/MIC ≥75, and C_{min} ≤2.5 mg/L [16–18]. For gentamicin, main PK/PD targets were C_{max}/MIC between 8 and 10, considering an MIC ranging from 1 to 2 mg/L [23–27].

As for tobramycin, C_{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_{min} values were set to be ≤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 Vd [15]. Although median CL and Vd 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 Vd 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 Vd [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 Vd.

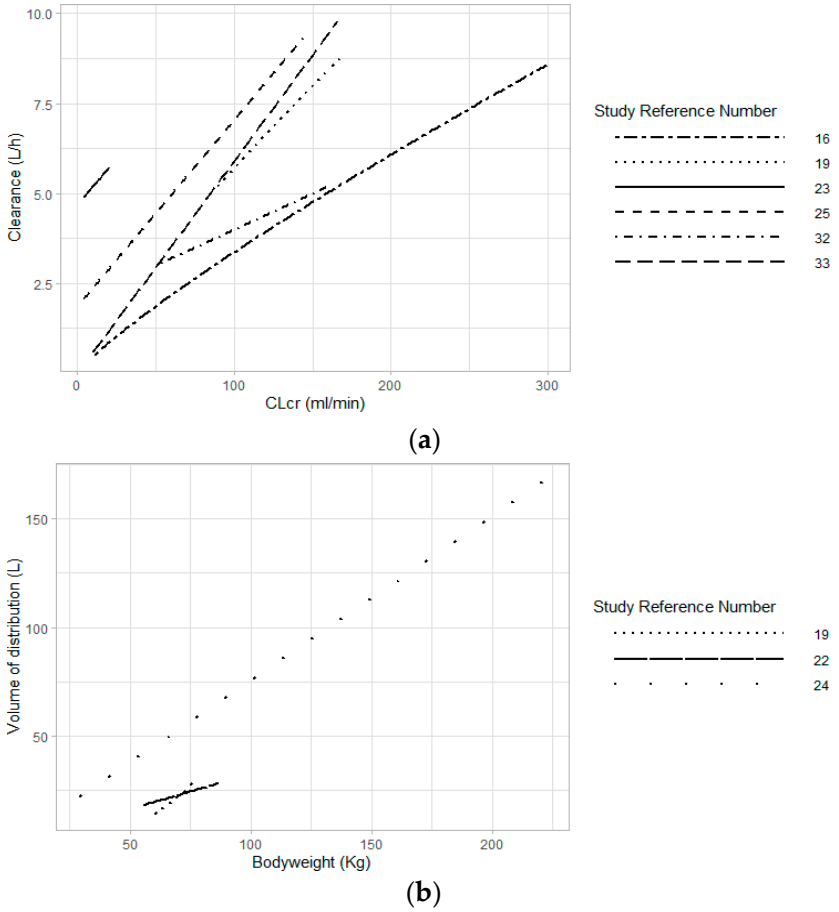

Figure 3. (**a**) Aminoglycoside clearanc e values against range of creatinine clearance in the respective studies. (**b**) Aminogly coside volume of distribut ion v alues against range of bo dyw eight in the respective studies. Note: Two studies used IBW [19,26] and one used TBW [24] in their model.

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 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 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 $C_{max} \geq 64$ mg/L and $AUC_{0-24} \geq 600$ mg*h/L compared to the conventional 30 mg/kg of corrected bodyweight (CBW), considering 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, CL_{CG} (10 mL/min to 250 mL/min), and BSA (1.5 m^2 to 2.5 m^2). As for Aréchiga-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 CL_{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 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 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_{max}/MIC 8 and AUC_{0-24} 70 or AUC_{0-24} 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 $C_{max} > 10$ mg/L, $C_{trough\ at\ 24h} < 1$ mg/L, and 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 AUC with daily fixed dosages of 375 and 400 mg. The other study from Aarons et al. simulated dosing regimens on the basis of CL_{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 CL_{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 $C_{max} \geq 8$ mg/L and 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.

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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. Buijk, S.; Mouton, J.; Gyssens, I .; Verbr ugh, H .; Br uining, H. Experience with a once- daily dosing progr am of aminoglyc osides in critically ill patients. *Intensive 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. *Pharmacother. 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. Eliopo ulos , G.M.; Drusano, G.L.; Ambros e, P.G.; Bhav nani, S.M.; Bertino, J.S.; N afziger, A.N.; Louie, A. Back to the Futur e: 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.; T aiber g, 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.; v an Gelder , T.; Koch, B.C.P. Clinic al applic ations of population phar macokinet ic models of antibiotics: Challenges and perspectives. *Pharmacol. Res.* **2018**, *134*, 280–288. [CrossRef]
12. Lover n, M.; Sar gentini- Maier, M.-L.; Otoul, C.; Watelet, J.-B. Population phar macokinetic and phar macodynamic analy sis in allergic diseases. *Drug Metab. Rev.* **2009**, *41*, 475–485. [CrossRef] [PubMed]
13. Kanji, S.; H ay es, M.; Ling, A.; Shamseer, L.; Chant, C.; Edw ar ds, D.J.; Edw ards, S.; Ensom, M.H .H.; Foster , D.R.; H ardy, B.; et al. Reporting Guidelines for Clinical Phar macokinetic Studies: T he ClinPK Statement. *Clin. Pharmacokinet.* **2015**, *54*, 783– 795. [CrossRef] [PubMed]
14. Moher, D.; Liberati, A.; T etzlaff, J.; Alt man, D.G.; Group, P. Preferred r eporting items for systematic r eviews and meta- analys es: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef] [PubMed]
15. Marsot, 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.; Bour guignon, L.; Cohen, S.; Roger , C.; Lefrant, J.- Y.; Roberts, J.A.; All aouchiche, B.; Lepape, A.; Friggeri, A.; Goutell e, S. Amikacin Initial Dose in Critical ly Ill Patients: A Nonpar ametric Approach To Optimize a Prior i Phar macokinetic/Pharmacodynamic T arget Attainments in Individual Patients. *Antimicrob. Agents Chemother.* **2019**, *63*, e00993-19. [CrossRef] [PubMed]
17. Roger , C.; Wallis, S.C.; Mull er, L.; Saissi, G.; Lipman, J.; Lefrant, J.- Y.; Roberts, J.A . Influenc e of Renal Repl acement Modalit ies on Amikacin Population Phar macokinetics in Critical ly Ill Patients on Continuous Renal Replacement Ther apy . *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 Suitabil ity of Standard Dosing Regimens of Amikacin in Critical ly Ill Patients w ith Open-Abdomen and N egativ e- Pressur e Wound Therapy. *Antimicrob. Agents Chemother.* **2020**, *64*, e02098-19. [CrossRef]
19. Aréchiga-A lv ar ado, N.A.; Medell ín-Gar ibay , S.E.; Milán-Segovia, R.d.C.; Ortiz-Álvar ez, 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]
20. Petitcol lin, A.; Dequin, P.F.; Darrouzain, F.; Vecellio, L.; Boulain, T .; Gar ot, D.; Paintaud, G.; T er nant, D.; Ehr mann, S. Phar macokinetics of high-dose nebuliz ed amikacin in v entilated critically il l patients. *J. Antimicrob. Chemother.* **2016**, *71*, 3482–3486. [CrossRef]
21. French, M.A.; Cerra, F.B.; Plaut, M.E.; Schentag, J.J. Amikacin and gentamicin accumulatio n phar macokinetics and nephrotoxicity in critically ill patients. *Antimicrob. Agents Chemother.* **1981**, *19*, 147–152. [CrossRef] [PubMed]
22. Hodiamont, C.J.; Juffer mans, N.P.; Bouman, C.S.C.; de Jong, M.D.; Mathôt, R.A.A.; v an H est, R.M. Determinants of gentamicin concentrations in critical ly ill patients: A population phar macokinetic 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 Critical ly Ill Pat ients. *Ther. Drug Monit.* **2008**, *30*, 674–681. [CrossRef] [PubMed]
25. Bos, J.C.; Prins, J.M.; Mistício, M.C.; N unguiane, G.; Lang, C.N .; Beirã o, J.C.; Mathôt, R.A.A.; v an H est, R.M. Population Phar macokinetics with Monte Carlo Simulations of Gentamicin in a Population of Sev er ely Ill Adult Patients from Sub- Sahar an Africa. *Antimicrob. Agents Chemother.* **2019**, *63*, e02328-18. [CrossRef]
26. Hodiamont, C.J.; Janssen, J.M.; de Jong, M.D.; Mathôt, R.A.; Juffer mans, N.P.; v an H est, R.M. T herapeutic Dr ug Monitor ing 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 diafiltratio n in critically ill patients with acute kidney injury. *Antimicrob. Agents Chemother.* **2010**, *54*, 3635–3640. [CrossRef]
28. Barletta, J.F.; Johnson, S.B.; N ix, D.E.; Nix, L.C.; Erstad; Brian, L. Population Phar macokinetics of Aminogly cosides in Critical ly Ill Trauma Patients on Once-Daily Regimens. *J. Trauma Acute Care Surg.* **2000**, *49*, 869–872. [CrossRef]

29. Gomes, A.; van der Wijk, L.; Proost, J.H.; Sinha, B.; Touw, D.J. Pharmacokinetic modeling of gentamicin in treatment of infective endocarditis: Model development and validation of existing models. *PLoS ONE* **2017**, *12*, e0177324. [CrossRef]
30. Watling, S.M.; Kisor, D.F. Population Pharmacokinetics: Development of a Medical Intensive Care Unit-Specific Gentamicin Dosing Nomogram. *Ann. Pharmacother.* **1993**, *27*, 151–154. [CrossRef]
31. Kisor, D.F.; Watling, S.M.; Zarowitz, B.J.; Jelliffe, R.W. Population Pharmacokinetics of Gentamicin. *Clin. Pharmacokinet.* **1992**, *23*, 62–68. [CrossRef] [PubMed]
32. Conil, J.- M.; Georges, B.; Ruiz, S.; Riv al, T .; Seguin, T .; Cougot, P.; Fourcade, O.; Phar md, G.H.; Saivin, S. Tobr amycin disposition in ICU patients r eceiving a once daily regimen: Population approach and dosage s imulations. *Br. J. Clin. Pharmacol.* **2011**, *71*, 61–71. [CrossRef] [PubMed]
33. Aarons, L.; Vozeh, S.; Wenk, M.; Weiss, P.; Foll ath, F. Population phar macokinetics of tobr amycin. *Br. J. Clin. Pharm.* **1989**, *28*, 305–314. [CrossRef] [PubMed]
34. Hennig, S.; Standing, J.F.; Staatz, C.E.; Thomson, A.H. Population Pharmacokinetics of Tobramycin in Patients with and without Cystic Fibrosis. *Clin. Pharmacokinet.* **2013**, *52*, 289–301. [CrossRef]
35. Bilbao-Meseguer, I.; Rodríguez-Gascó n, A.; Barrasa, H.; Isla, A.; Solinís, M.Á. Augmented Renal Clear ance in Critically Ill Patients: A Systematic Review. *Clin. Pharmacokinet.* **2018**, *57*, 1107–1121. [CrossRef] [PubMed]
36. Bagshaw, S.M.; Uchino, S.; Bellomo, R.; Morimatsu, H.; Morgera, S.; Schetz, M.; T an, I.; Bouman, C.; Macedo, E.; Gibney, N.; et al. Septic Acute Kidney Injury in Critically Ill Patients: Clinic al Characteristics and Outcomes. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 431. [CrossRef] [PubMed]
37. Lode, H .; Gr unert, K.; Koeppe, P.; Langmaack, H . Pharmacokinetic and Clinic al Studies with Amikacin, a New Aminoglyco side Antibiotic. *J. Infect. Dis.* **1976**, *134*, S316–S322. [CrossRef]
38. Demczar, D.J.; N afziger, A.N.; Bertino, J.S., Jr . Pharmacokinetics of gentamicin at traditional v ersus high doses: I mplic ations for once-daily aminoglycoside dosing. *Antimicrob. Agents Chemother.* **1997**, *41*, 1115–1119. [CrossRef]
39. Garr affo, R.; Dr ugeon, H .B.; Dell amonica, P.; Bernard, E.; Lapalus, P. Deter mination of optimal dosage regimen for amikacin in healthy volunt eers by study of phar macokinetics and bactericidal activ ity. *Antimicrob. Agents Chemother.* **1990**, *34*, 614–621. [CrossRef]
40. Green, T.P.; Mirkin, B.L.; Peterson, P.K.; Sinaiko, A.R.; Ramsay, N.K.C.; O'Dea, R.F. Tobramycin Serum Level Monitoring in Young Patients with Normal Renal Function. *Clin. Pharmacokinet.* **1984**, *9*, 457–468. [CrossRef]
41. Lim, A.K.H.; Mathanasenarajah, G.; Larmour, I. Assessment of aminoglycoside dosing and estimated glomerular filtration rate i n determining gentamicin and tobramycin area under the curve and clearance. *Intern. Med. J.* **2015**, *45*, 319–329. [CrossRef]
42. Chin, P.K.L.; F lorkow ski, C.M.; Begg, E.J. The per for mances of the Cockcr oft -Gault, Modification of Diet in Renal Disease Study and Chronic Kidney Disease Epidemiology Coll aboration equations in pr edicting gentamicin clearance. *Ann. Clin. Biochem.* **2013**, *50*, 546–557. [CrossRef]
43. Pai, M.P.; Nafziger , A.N.; Bertino, J.S. Simplified Estimation of Aminoglyc oside Phar macokinetics in Underw eight and Obes e Adult Patients. *Antimicrob. Agents Chemother.* **2011**, *55*, 4006. [CrossRef] [PubMed]
44. Sunder , S.; Jayar aman, R.; Mahapatra, H .S.; Sathi, S.; Ramanan, V.; Kanchi, P.; Gupta, A.; Daksh, S.K.; Ram, P. Estimation of r enal function in the intensive care unit: The covert concepts brought to light. *J. Intensive Care* **2014**, *2*, 31. [CrossRef] [PubMed]
45. Ruiz, S.; Minv ill e, V.; Asehnoune, K.; Virtos , M.; Geor ges, B.; Fourcade, O.; Conil, J.- M. Scr eening of patients with augmented renal clearanc e in ICU: Taking into account the CKD-EPI equation, the age, and the cause of admission. *Ann. Intensive Care* **2015**, *5*, 49. [CrossRef]
46. Bragadottir, G.; Redfors, B.; Ricksten, S.- E. Assessing glomer ular filtr ation r ate (GFR) in cr itically ill patients with acute kidney injury—True GFR versus urinary creatinine clearance and estimating equations. *Crit. Care* **2013**, *17*, R108. [CrossRef]
47. Grootaert, V.; Will ems, L.; Debav ey e, Y.; Mey froidt, G.; Spriet, I. Augmented Renal Clear ance in the Critically Ill: How to Assess Kidney Function. *Ann. Pharmacother.* **2012**, *46*, 952–959. [CrossRef] [PubMed]
48. Ciarimbo li, G.; Lancaster, C.S.; Schlatter, E.; Fr anke, R.M.; Sprowl, J.A.; Pavenstädt, H.; Massmann, V.; Guckel, D.; Mathijssen, R.H.J.; Yang, W.; et al. Proximal tubular secretion of creatinine by organic cation transporter OCT2 in cancer patients. *Clin. Cancer Res.* **2012**, *18*, 1101–1108. [CrossRef]
49. Zarow itz, B.J.; Robert, S.; Peterson, E.L. Pr ediction of G lo mer ular Filtration Rate Using Aminoglyc oside Clearance in Critically Ill Medical Patients. *Ann. Pharmacother.* **1992**, *26*, 1205–1210. [CrossRef]
50. Mangoni, A.A.; Jackson, S.H.D. Age-relat ed changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *Br. J. Clin. Pharm.* **2004**, *57*, 6–14. [CrossRef]
51. Triggs, E.; Charles, B. Pharmacokinetics and Therapeutic Drug Monitoring of Gentamicin in the Elderly. *Clin. Pharmacokinet.* **1999**, *37*, 331–341. [CrossRef] [PubMed]
52. Bauer, L.A.; Blouin, R.A. Gentamicin Pharmacokinetics. *J. Am. Geriatr. Soc.* **1982**, *30*, 309–311. [CrossRef]
53. Matzke, G.R.; Jameson, J.J.; Halstenson, C.E. Gentamicin Disposition in Young and Elderly Patients with Various Degrees of Renal Function. *J. Clin. Pharmacol.* **1987**, *27*, 216–220. [CrossRef] [PubMed]
54. Velissaris, D.; Karamouzos, V.; Marangos, M.; Pierrakos, C.; Karanikolas, M. Pharmacokinetic changes and dosing modification of aminoglycosides in critically ill obese patients: A literature review. *J. Clin. Med. Res.* **2014**, *6*, 227–233. [CrossRef]
55. Pai, M.P. Anti-infective Dosing for Obese Adult Patients: A Focus on Newer Drugs to Treat Methicillin-resistant Staphylococcus aureus Acute Bacterial Skin and Skin Structure Infections. *Clin. Ther.* **2016**, *38*, 2032–2044. [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*, 745.e7–745.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.; Stryjewski, 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 bas ed on observations for external model evaluatio n of population analyses. *J. Pharm. Pharm.* **2010**, *37*, 49–65. [CrossRef] [PubMed]
62. Guo, T.; v an H est, R.M.; Roggev een, L.F.; Fleuren, L.M.; T hor al, P.J.; Bosman, R.J.; v an der Voort, P.H .J.; Girbes, A.R.J.; Mathot, R.A.A.; El bers , P.W.G. Exter nal Ev aluation of Population Pharmacokinetic Models of Vancomycin in Lar ge Cohorts of I ntensiv e 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 ev aluation of pop ulation phar macokinetic models for continuous administration of meropenem in critically ill adult patients. *Eur. J. Clin. Pharmacol.* **2020**, *76*, 1281–1289. [CrossRef]
64. Bukkems, L.H .; Roger , C.; Hodiamont, C.J.; Lefr ant, J.- Y.; Juffermans, N.P.; Ro berts , J.A .; v an H est, R.M. Pr edictiv e perfor mance of a gentamicin population pharmacokinetic model in tw o w ester n populations of critical ly 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]

Supplementary Information:

Table S1 : Checklist of information to be includedwhenreporting a clinical pharmacokinetic study basedon *ClinPK* [13]

Drug	Study	Title/Abstract		Background			Methods										Results						Discussion/Conclusion		Other Information
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Amikacin	Boidin C [16]	●	●	●	●	●	●	○	●	○	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	○
	Roger C [17]	●	●	●	●	●	●	○	●	●	●	●	●	○	●	●	○	○	●	●	●	NA	●	●	●
	Carrié C [18]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	●	NA	●	●	●
	Aréchiga-Alvarado NA [19]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	Petitcollin A [20]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	French MA [21]	●	●	●	●	●	●	●	○	○	○	●	○	○	●	●	○	○	●	●	NA	NA	●	●	●
Gentamicin	Hodiamont CJ [22]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	●	NA	●	●	●
	Teigen MM [23]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	●	NA	●	●	●
	Rea RS [24]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	Bos JC [25]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	Hodiamont CJ [26]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	Roberts JA [27]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	●	NA	●	●	●
	Barletta JF [28]	●	●	●	●	●	●	○	○	●	○	●	●	●	●	●	○	○	●	●	NA	NA	○	●	○
	Gomes A [29]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	Watling SM [30]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	○
	Kisor DF [31]	●	●	●	●	●	●	○	○	●	●	●	○	●	●	●	○	○	●	●	NA	NA	●	●	○
	French MA [21]	●	●	●	●	●	●	●	○	○	○	●	○	○	●	●	○	○	●	●	NA	NA	●	●	●
Tobramycin	Conil JM [32]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	Aarons L [33]	●	●	●	●	●	●	○	○	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●
	Hennig S [34]	●	●	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	NA	NA	●	●	●

● Information included
○ Information not includedor not found
NA: Not Applicable

Table S2: Characteristics of the populationpharmacokineticmodels developed by the studiesincludedin thisreview (one compartment)

Drug	Study	CL (L/h)			V_d (L)			K_{el}			IIV		RV		
		Formula	Parameter	Value	Formula	Parameter	Value	Formula	Parameter	Value	CL (%)	V_d (%)	Exponentia	Proportional	Additive
Amikacin	Aréchiga-Alvarado NA [19]	$CL=\theta_1 X (CL_{CR}/130)^{\theta 3}$	θ_1	7.1	$V_d = \theta_2 X (IBW/68)^{\theta 4}$	θ_2	20.3	NR	NR	NR	27.2	33.6	–	–	1.78 mg/L
			θ_3	0.84		θ_4	2.94								
Gentamicin	Teigen MM [23]	$CL_{NHD} = \theta_1 X (CL_{CR}/0.53)$	θ_1	0.453	$V_d = \theta_3$	θ_3	23.5	NR	NR	NR	$\omega^2 = 0.264$	$\omega^2 = 0.0256$	–	0.0804[a]	0.00659[a]
		$CL_{HD} = \theta_2$	θ_2	4.69											
	Rea RS [24]	$CL= (\theta_{1\_CLMAX} X GFR^{1.2})/(\theta_{2\_EGFRHILL50} + GFR^{1.2})$	θ_{1_CLMAX}	3.14	$V_d = \theta_3 X (BW/70)$	θ_3	53	NR	NR	NR	83.7	64.4	–	24.3	0.381 µg/mL
			$\theta_{2\_EGFRHILL50}$	54.8											
	Bos JC [25]	$CL=\theta_1 X (1 + \theta_{2\_Factor\ associating\ Gentamicin\ CL\ and\ CLcr} X (CL_{CR} -74)$	θ_1	5.7	NR	V_d	19	NR	NR	NR	74	49	–	32	0.056 mg/L
			$\theta_{2\_Factor\ associating\ Gentamicin\ CL\ and\ CLcr}$	0.0091											
	Barletta JF [28]	NR	CL	5.41	NR	V_d	Gentamicine:34.3 Tobramycine : 17.3	NR	NR	NR	29.3	11.9	–	–	144%
	Gomes A [29]	NR	CL_{fr} [b]	0.698	NR	V_d	0.312 L/kg LBMc	NR	NR	NR	NR	NR	NR	NR	NR
	Watling SM [30]	NR	NR	NR	NR	V_d	0.34 L/Kg	$K_{el}= \theta_{KS} X CL_{CR} + \theta_{Ki}$	θ_{KS}	0.00218	NR	NR	NR	NR	NR
								NR	θ_{Ki}	0.007					
	Kisor DF [31]	NR	CL	3.01	NR	V_d	0.376 L/kg	NR	K_{el}	0.203	NR	NR	NR	NR	NR

BWBody Weight, *CL* Clearance, *CLcr* Creatinine Clearance (mL/min/m2), CL_{HD} Hemodialysis Clearance, CL_{MAX} *Maximum Clearance*, CL_{NHD} Non hemodialysis Clearance, *EGFRHILL50* GFR yielding half of CLMAX (mL/min), *GFR* Glomerular Filtrationrate (mL/min) ,*IBW* Ideal Body Weight, *IIV* Interindividual variation, K_d Elimination Constant, K_S K Slope, K_i Intercept, *LBMc* Lean body mass according to the equation of Chennavasin corrected for fat distribution, *NR* Not Reported, *RV* Residual Variability, Vd Volume of Distribution

[a] Variance

[b] renal gentamicinclearance asa fraction of creatinine clearance

[c] PKModel was constructed withsamplesfrom Gentamicinand Tobramycin

Table S3: Characteristics of the populationpharmacokineticmodelsdeveloped by the studiesincludedin thisreview (two-compartment)

Drug	Study	CL (L/h)			V_1 (L)			V_2 (L)			K_{el}		
		Formula	Parameter	Value	Formula	Parameter	Value	Formula	Parameter	Value	Formula	Parameter	Value
Amikacin	Boidin C [16]	$CL = \theta_1 X (CL_{CG}/73.6)^{\theta 2}$	θ_1	2.6	$V_1 = \theta_3 X (BSA/1.93)$	θ_3	23	$V_1 = V_2$	V_2	23	NR	NR	NR
			θ_2	0.85									
	Roger C [17]	$CL = \theta_{CLHF} X [(TBW/80)^{0.75}] + \theta_{CLHDF} X [(TBW/75)^{0.75}]$	θ_{CLHF}	4.69	NR	V_1 (central)	25.2	NR	NR	NR	NR	NR	NR
			θ_{CLHDF}	4.45									
	Carrié C [18]	$CL = \theta_{CLpop} X (CL_{CR}/66.7)^{0.69}$	θCLpop	NR	$V_1 = \theta_{V1pop} X (CL_{CR}/66.7)^{0.22} X (ABW/79.6)^{0.48}$	θ_{V1pop}	NR	NR	$V_{n\text{-}crrt}$	11.7	NR	NR	NR
			$CL_{n\text{-}crrt}$	3.02	NR	$V_{n\text{-}crrt}$	23.2	NR	V_{crrt}	14.1			
			CL_{crrt}	2.32	NR	V_{crrt}	25.5						
	Petitcollin A [20]	NR	CL	4.98	NR	Vc	10.2	NR	V_2	14.98	NR	K_{10}	0.488
	French MA [21]	NR	TBCL	33.45[d]	NR	Vc	0.305 L/Kg	NR	NR	NR	NR	K_{10}	0.1
Gentamicin	Hodiamont CJ [22]	$CL = \theta_{noCVVH} X (IBW/70)^{0.75}$	θ_{noCVVH}	1.15	$V_1 = \theta_1 X (IBW/70) X (ALBM/22)^{-0.833}$	θ_1	21.2 L/70 Kg	NR	V_2	18.4 L/70 kg	NR	NR	NR
		$CL = \theta_{CVVH} X (IBW/70)^{0.75}$	θ_{CVVH}	2.13									
	Hodiamont CJ [26]	NR	CL	2.3	NR	V_1	21.6	NR	V_2	10.2	NR	NR	NR
	Roberts JA [27]	$TVCL_{NEDD\text{-}f} = \theta_1 X (LBW/55) X FCR$	$CL_{EDD\text{-}F}$	2.59	NR	Vc	14.1	NR	Vp	32.8	NR	NR	NR
		$TVCL = TVCL_{NEDD\text{-}f} + TVCL_{EDD\text{-}f}$	$CL_{NEDD\text{-}F}$	0.24									
			TVCL	2.83									
	French MA [21]	NR	TBCL	29.53 [d]	NR	Vc	0.257 L/Kg	NR	NR	NR	NR	K_{10}	0.18
Tobramycin	Conil JM [32]	$TVCL = \theta_1 + (\theta_2 X (COCK-94)) + (\theta_3 X (HEIG-172))$	θ_1	3.83	$TVV_1 = \theta_4$	θ_4	25.5	NR	NR	NR	NR	NR	NR
			θ_2	0.02									
			θ_3	0.052									
	Aarons L [33]	CL = θ1 X CLCR	θ_1	0.059 [e]	NR	V_1	0.327	NR	NR	NR	NR	NR	NR
	Hennig S [34]	$CL\_f/m = \theta_{CL\_f/m} x (FFM/70)^{0.952} x [1 + \theta_{AGE} x (AGE - 18)] x (SCRmean/SCR)^{0.222}$	θ_{CL_f}	8.1 L/h/70 Kg	$V_1 (f/m) = \theta_{V1,f/m} x (FFM/70)$	θ_{V1_f}	20.2 L/70 Kg	$V_2 = \theta_{V2} X (FFM/70)^{\theta FFM}$	θ_{V2}	10.0 L/70 Kg	NR	NR	NR
			θ_{CL_m}	9.5 L/h/70 Kg		θ_{V1_m}	25.2 L/70 Kg		θ_{FFM}	0.975			
			θ_{Age_u18}	-0.021									
			θ_{Age_o18}	-0.01									

ABW Adjusted Bodyweight, *ALBM* Albumine level, *Age_o18* Age over 18 years old, *Age_u18* Age under 18 years old, *BSA Body Surface Area*, CL_{CG} or CL_{CR} or *COCK* Creatinine clearance estimated by the original Cockcroft-Gault Equation, CL_{CRRT} Clearance of patients under CRRT (Continuous renal replacement therapy), CL_{CVVH} Clearance when patient is on CVVH (continuous venovenous haemofiltration), $CL_{EDD\text{-}f}$ Clearance when patient is on EDD-f (extended daily diafiltration) , *CLHDF* Clearance on hemodiafiltration, *CLHF* Clearance on hemofiltration, $CL_{NEDD\text{-}f}$ Clearance when patient is not on EDD-f, CL_{noCVVH} Clearance when patient is off CVVH, $CL_{n\text{-}CRRT}$ Clearance of patients not under CRRT, *CL_f* Clearance if patient is female, *CL_m* Clearance if patient is male, *FCR* Inverse of the final plasma creatine concentration recorded in µmol/L before commencement of EDD-f, *FFM* Fat-free mass, *HEIG* Height, *IBW* Ideal Bodyweight, *Q* Intercompartment clearance, *TBCL* Total Body Clearance, *TBW* Total Bodyweight, *V1_f* Apparent Volume of distribution of the central compartment if patient is female, *V1_m* Apparent Volume of distribution of the central compartment if patient is male, V_1 *or Vc* central volume, V_{CRRT} distribution volume of patients under CRRT, $Vn\text{-}_{CRRT}$ distributionvolume of patients not under CRRT, *Vp* peripheral volume

[a] Of note, the author set the peripheral volume V_2 equal to V_1.

[b] Coefficient of variation, calculated asthe square root of $(e^{\omega}-1)*100\%$

[c] Variance of the residual error

[d] Estimated asml/min

[e] Proportionality constant relating creatinine clearance (ml/min) to drug clearance (L/h)

Table S3: Characteristics of the populationpharmacokinetic modelsdeveloped by the studiesincluded in thisreview (two-compartment) (continued)

Drug	Study	Q (L/h)			K_{12} (h^{-1})			K_{21} (h^{-1})			IIV				RV		
		Formula	Parameter	Value	Formula	Parameter	Value	Formula	Parameter	Value	CL (%)	V_1 (%)	V_2 (%)	Q (%)	Exponential (%)	Proportional(%)	Additive (mg/L)
Amikacin	Boidin C [16]	NR	θ_4	0.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Roger C [17]				NR	K_{12} (cp)	0.89	NR	K_{21} (pc)	2.38	NR	NR	NR	NR	NR	NR	NR
	Carrié C [18]	NR	$Q_{n\text{-}crrt}$	1.05	NR	NR	NR	NR	NR	NR	$\omega^2_{n\text{-}crrt}$ = 0.345	$\omega^2_{n\text{-}crrt}$ = 0.047	$\omega^2_{n\text{-}crrt}$ = 0.695	$\omega^2_{n\text{-}crrt}$ = 0.813	–	N-CRRT = 0.132	–
			Q_{crrt}	1.19							ω^2_{crrt} = 0.221	ω^2_{crrt} = 0.081	ω^2_{crrt} = 0.380	ω^2_{crrt} = 0.418 L/h		CRRT = 0.232	
	Petitcollin A [20]	NR	Q	12.85	NR	K_{12}	1.26	NR	K_{21}	0.858	NR	NR	NR	NR	–	10.9	0.214
	French MA [21]				NR	K_{12}	0.016	NR	K_{21}	0.005	NR	NR	NR	NR	NR	NR	NR
Gentamicin	Hodiamont CJ [22]	NR	Q	1.96*	NR	NR	NR	NR	NR	NR	CL_{noCVVH} = 42.5 [b]	17.2	NR	NR	–	33.8	–
											CL_{CVVH} = 29.5 [b]		NR	NR			
	Hodiamont CJ [26]	NR	Q	1.3	NR	NR	NR	NR	NR	NR	75.0 [b]	27.0 [b]	NR	NR	–	19.4	0.13
	Roberts JA [27]	NR	Q	2.76	NR	NR	NR	NR	NR	NR	39.9 [b]	16.4 [b]	20.5 [b]	110.5 [b]	–	20.8	–
	French MA [21]	NR	NR	NR	NR	K_{12}	0.025	NR	K_{21}	0.01	NR	NR	NR	NR	NR	NR	NR
Tobramycin	Conil JM [32]	NR	NR	NR	NR	NR	NR	NR	NR	NR	ω^2 =0.095	ω^2 = 0.045	Fixed	Fixed	–	0.056 [c]	–
	Aarons L [33]	NR	NR	NR	NR	K_{12}	0.012	NR	K_{21}	0.027	32	3	NR		–	21	–
	Hennig S [34]	Q = θ_Q X (FFM/70)$^{\theta FFM}$	θ_Q	1.5*	NR	NR	NR	NR	NR	NR	CL_m = NR	V_{1_m} = NR	58.5	41.8	–	20.4	–
			θ_{FFM}	0.975							CL_f = 25.9	V_{1_f} = 15.2					

ABW Adjusted Bodyweight, *ALBM* Albumine level, *Age_o18* Age over 18 years old, *Age_u18* Age under 18 years old, *BSA Body Surface Area*, CL_{CG} or CL_{CR} or *COCK* Creatinine clearance estimated by the original Cockcroft-Gault Equation, CL_{CRRT} Clearance of patients under CRRT (Continuousrenalreplacement therapy), CL_{CVVH} Clearance whenpatient is on CVVH (continuous venovenous haemofiltration), $CL_{EDD\text{-}f}$ Clearance whenpatient is on EDD-f (extended daily diafiltration) , *CLHDF* Clearanceon hemodiafiltration, *CLHF* Clearance on hemofiltration, $CL_{NEDD\text{-}f}$ Clearance when patient is not on EDD-f, CL_{noCVVH} Clearance when patient is off CVVH, $CL_{n\text{-}CRRT}$ Clearance of patients not under CRRT, *CL_f* Clearance if patient is female, *CL_m* Clearance if patient is male, *FCR* Inverse of the final plasma creatine concentration recorded in µmol/L before commencement of EDD-f, *FFM* Fat-free mass, *HEIG* Height, *IBW* Ideal Bodyweight, *Q* Intercompartment clearance, *TBCL* Total Body Clearance, *TBW* Total Bodyweight, *V1_f* Apparent Volume of distribution of the central compartment if patient is female, *V1_m* Apparent Volume of distribution of the central compartment if patient is male, V_1 *or Vc* central volume, V_{CRRT} distributionvolume of patients under CRRT, *Vn-CRRT*distributionvolume of patientsnot under CRRT, *Vp* peripheral volume

[a] Of note, the author set the peripheral volume V_2 equal to V_1.

[b] Coefficient of variation, calculated asthe square root of (e^{ω}-1)*100%

[c] Variance of the residual error

[d] Estimated asml/min

[e] Proportionality constant relating creatinine clearance (ml/min) to drug clearance (L/h)

[*] L/h/70 kg

Table S4. 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-t0}	LBW	LBMc	FFM	BSA	BMI	SCr	hemoglobin	Salb	CL_{CG}	CL_{hf}	CL_{hdf}	$CL_{CKD-EPI}$	CL_{MDRD}	CalcCL$_{CR}$	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]																														
	French MA [i] [21]																														
Tobramycin	Conil JM [32]			●						○							○			○											
	Aarons L [33]								○											●											
	Hennig S [34]	●	○	○					○					●			●			○											

ADJ Adjusted body weight, ALAT Alanine amino transferase, APACHE II Acute Physiology andchronichealthevaluation II, *ARC* Augmented renal clearance (ARC) defined asa CLCR ≥ 130 mL/min, *ASAT* Aspartate amino transferase, *BMI* Body Mass Index, *BSA* Body Surface Area, *BUN* Blood Urea Nitrogen, BW_{AD-t0} 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* Correctedbody weight, *CF* Cystic Fibrosis, *CLCKD-EPI* Creatinine clearance estimatedwith CKD-EPI, *CLCG* Creatinine Clearance estimated by Cockcroft-Gault equation, CL_{hdf} 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* Continuousvenovenous haemofiltration, *EDD-f* Extended daily diafiltration, *FCR* Inverse of the final plasmacreatine concentration recordedin 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* Glomerual filtration rate, GFR_{MDRD} GFR estmatedby the equation fro the Modification of Diet in Renal Disease, $GFR_{CKD-EPI}$ GFRestimated 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-relatedorgan failure assessment score

● Tested and significant

○ Tested and not significant

[a] Adjusted body weight (ABW) was determined as follows : i) for BMI ≤ 30 kg/m², ABW = TBW; ii) for BMI > 30 kg/m², ABW= ideal body weight (IBW) + 0.43 (TBW - IBW), with IBW calculatedaccording to the Lorenz formula [74]

[b] Adjusted body weight wascalculated as proposed by Bauer et al.: AdjBW = 0.4(TBW-IBW) +IBW for morbidly obese patients(IBW/TBWratio of ≥ 1.9)

[c] Adjusted body weight proposed by Traynoret al. Was adaptedaccording to French recommendationswitha weight correctionfactor for overweight patients (IBW/TBWratioof ≥ 1.25) andcalculatedas CBW = 0.43 (TBW-IBW)+IBW

[d] Described as Actualbody weight

[e] Modified SOFA score (without neurologicand 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 thisstudy

Table S4. Covariates that were included or evaluated for inclusion by the population pharmacokinetic models included in this review (continued).

Drug	Study	Tested and significantcovariates																			
		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 parental nutrition	Flow rate of ultrafiltrate during CVVH	Residual Renal function	Filter age	$Fluid_{NPT}$	Hemodialysis
Amikacin	Boidin C [16]	○	○		○	○															
	Roger C [17]																○	○			
	Carrié C [18]	○ [e]											○						○		
	Aréchiga-Alvarado NA [19]			○			○	○	○	○		○									
	Petitcollin A [20]																				
	French MA [i] [21]																				
	Hodiamont CJ [22]			○							○		○	○	○	○					
	Teigen MM [23]																				●
	Rea RS [24] Bos JC[25]																				
	Hodiamont CJ [26]																				
Gentamicin	Roberts JA [27]																				
	Barletta JF [28]																				
	Gomes A [29]																				
	Watling SM [30]																				
	Kisor DF [i] [31]																				
	French MA [i] [21]																				
	Conil JM [32]							○													
Tobramycin	Aarons L [33]																				
	Hennig S [34]																				

ADJ Adjusted body weight, *ALAT Alanine amino transferase*, *APACHEII* Acute Physiology and chronic health evaluation II, *ARC* Augmentedrenal 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-I0} 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_{hdf} total amikacin clearance on hemodiafiltration, CL_{hf} total amikacin clearance on hemofiltration, CL_{MDRD} Creatinine clearance calculatedwith 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 µmol/Lbefore commencement of EDD-f, *FFM* Fat free mass, $Fluid_{NPT}$ Amount of fluids collected by the NPT over the sampling day, *GFR* Glomerual filtration rate, GFR_{MDRD} GFR estmated by the equation fro 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 massaccording 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 organfailure assessment score

● Tested and significant

○ Tested and not significant

[a] Adjusted body weight (ABW) was determined as follows : i) for BMI ≤ 30 kg/m², ABW = TBW; ii) for BMI > 30 kg/m², ABW= ideal body weight (IBW) + 0.43 (TBW - IBW), with IBW calculated according to the Lorenz formula[74]

[b] Adjusted body weight wascalculatedas proposedby 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 Actualbody weight

[e] Modified SOFA score (without neurologicand 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 thisstudy

Table S4. Covariates that were included or evaluated for inclusion by the population pharmacokinetic models included in this review (continued).

		Tested and significant covariates																		
												Usage of concomitant medication								
Drug	Study	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	Opioid analgesics	Cephalosporins	Diuretics	Antimycotics	Inotropics agents	Corticosteroids
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]																	
	French MA [i] [21]										●							
Tobramycin	Conil JM [32]	○	○	○														
	Aarons L [33]																	
	Hennig S [34]						○											

ADJ Adjusted body weight, *ALAT Alanine amino transferase*, *APACHEII* Acute Physiology and chronic health evaluation II, *ARC* Augmentedrenal 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-tbl} 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_{hdf} 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 venovenous haemofiltration, *EDD-f* Extended daily diafiltration, *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* Glomerual filtration rate, GFR_{MDRD} GFR estmated by the equation fro 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* Simplifiedacute physiology score II,*SCR* Serum Creatinine, *SOFA* Sepsis-relatedorgan failure assessment score

● Tested and significant

○ Tested and not significant

[a] Adjusted body weight (ABW) was determined as follows: i) for BMI ≤ 30 kg/m² , ABW = TBW; ii) for BMI > 30 kg/m², ABW= ideal body weight (IBW) + 0.43 (TBW - IBW), with IBW calculatedaccording to the Lorenz formula [74]

[b] Adjusted body weight wascalculated as proposed by Bauer et al.: AdjBW = 0.4(TBW-IBW) +IBW for morbidly obese patients(IBW/TBWratio 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 Actualbody weight

[e] Modified SOFA score (without neurologicand 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 thisstudy

Model validation

Before assessing that a Pop-PK model is accurate for a specific population of patients, several steps should be completed beforehand to evaluate the model.

Firstly, pharmacokinetic parameters from the model to be evaluated are to be used to predict the concentration at the same sampling times of the new dataset. Based on these predictions, in order to assess predictive performance, goodness-of-fit plots of the predicted concentration and observed concentration should be done. Secondly, as part of assessing predictive performance, different metrics should also be estimated based on prediction error (PE) [71]. The latter can be calculated from the following equation:

$$PE = \frac{C_{pred_i} - C_{obs_i}}{C_{obs_i}} \times 100\% \quad (1)$$

where C_{pred} and C_{obs} are the *i*th predicted and observed concentrations, respectively. In order to quantify bias, commonly used metrics are median or mean PE ($MDPE_i$) value based on the following equation:

$$MDPE_i\ (\%) = median\ or\ mean\ (PE_{ij}, j = 1,..., N_i) \quad (2)$$

From the values obtained for MADPE and MDPE, 95% confidence intervals should also be obtained to have a better overview of their plausible ranges. The 95% confidence intervals for MDPE should contain zero to be considered unbiased, whereas MADPE should be <20% to be deemed precise. The evaluation of these metrics also aims to determine if the Pop-PK model tends to under- or over-predict aminoglycosides concentrations. Considering that the consequences from an under-estimation of aminoglycosides concentrations (i.e. negative value of MDPE) could lead to nephrotoxicity and ototoxicity, the need of carefully evaluating a Pop-PK model before its application and generalization in other populations is even more crucial. On the other hand, an over-estimation of concentration could lead to a failure of reaching therapeutic targets of C_{max}/MIC for aminoglycosides.

Secondly, advanced internal validation, also known as interpolation, relies on simulations or subsets of the original dataset used for model building. Bootstraps, visual predictive checks (VPCs) or normalized prediction distribution error (NPDE) analysis are a few common strategies that should be considered to establish the overall fit of the Pop-PK model.

Article #3: EXTERNAL EVALUATION OF GENTAMICIN POPULATION PHARMACOKINETICS MODELS IN CRITICALLY ILL PATIENTS FROM QUEBEC

Alexandre Duong[1,2], Chantale Simard[3,4], David Williamson[1,5], , Amélie Marsot[1,2,6]

[1] Faculté de Pharmacie, Université de Montréal, Montréal, Canada; [2] Laboratoire de Suivi Thérapeutique Pharmacologique et Pharmacocinétique, Faculté de Pharmacie, Université de Montréal, Montréal, Canada; [3] Institut Universitaire de Cardiologie et Pneumologie de Québec, Québec, Canada; [4] Faculté de Pharmacie, Université de Laval, Québec, Canada; [5] Hôpital Sacré-Cœur de Montréal, Université de Montréal, Montréal, Canada; [6] Centre de Recherche, CHU Sainte Justine, Montréal, Canada

Nature de la contribution pour cet article : Conceptualisation, méthodologie (collecte de données, évaluation externe des modèles), analyse des résultats, rédaction et finalisation

Statut de l'article: En cours de révision par les co-auteurs et soumission au *Therapeutic Drug Monitoring*

N.B : Ce mémoire inclura seulement l'article présentant uniquement l'évaluation externe des modèles de gentamicine. Un autre article est présentement en cours de rédaction concernant l'évaluation externe des modèles de tobramycine. L'évaluation externe des modèles d'amikacine ne sera pas effectuée en raison du faible nombre de données récoltées pour cette molécule dans les deux établissements.

Abstract

Contexte Avant d'utiliser un modèle pharmacocinétique développé par approche populationnelle (PopPK) dans un contexte clinique réel, il est primordial d'évaluer la performance prédictive de ce modèle dans une population indépendante de celle qui a été utilisée pour le développement du modèle. En effet, cette méthode d'évaluation serait considérée comme la méthode la plus robuste pour évaluer un modèle. En raison de la grande variabilité inter- et intra-individuelle de la gentamicine au sein des patients aux soins intensifs, plusieurs modèles PopPK ont été développés, mais rare sont ceux qui ont été évalués façon externe. **Objectif** L'objectif de ce projet est d'évaluer les modèles PopPK de la gentamicine visant les patients aux soins intensifs avec deux populations provenant d'établissements québécois. **Méthodologie** Les données-patients ont été récoltées de façon rétrospective à l'Hôpital Sacré-Cœur de Montréal (HSCM) et l'Institut Universitaire de Cardiologie et Pneumologie de Québec (IUCPQ). Les modèles évalués proviennent d'une précédente revue de la littérature sur les modèles PopPK d'aminosides. L'évaluation externe a été effectuée sur le logiciel NONMEM® (version 7.5: ICON Development Solutions), et les valeurs de biais et d'imprécision ont été calculées. Des simulations de régimes posologiques ont été effectuées à partir du modèle le plus performant. **Résultats** La base de données de validation comprenait 39 et 48 patients de l'HSCM et l'IUCPQ, respectivement. L'ensemble des quatre modèles inclus dans l'évaluation externe ont respecté les critères de biais et d'imprécision. Des simulations ont été effectuées en utilisant le modèle de Bos et al., une administration uniquotidienne de 6-7 mg/kg considérant une CMI de 1 mg/L permettait d'optimiser l'atteinte des cibles d'efficacité. **Conclusion** Malgré que les quatre modèles ont respecté les critères d'évaluation de biais et d'imprécision, une importante variabilité est encore présente. Cette dernière pourrait être expliquée par les différentes caractéristiques démographiques entre la base de données de validation et les populations utilisées pour développer les modèles.

1. Introduction

Gentamicin is a broad-spectrum antibiotic from the aminoglycosides family mostly used against life-threatening infections due to suspected Gram-Negative bacteria (1, 2). Gentamicin's antimicrobial activity, along with other aminoglycosides, is concentration-dependent, therefore its efficacy is based on peak serum level (C_{max}) or area under the concentration curve (AUC) related to the minimal inhibitory concentration (MIC) (3). Moreover, due to the known potential ototoxicity and nephrotoxicity caused by aminoglycosides administration, therapeutic drug monitoring (TDM) is essential to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets while minimizing toxicity. In fact, considering the narrow therapeutic index of aminoglycosides, administration of aminoglycosides slowly shifted from multiple-daily dose (MDD) to once-daily dose (ODD) throughout the years (4, 5). In fact, the latter, also known as extended-interval dosing has shown better signs of minimizing toxicity, while also maintaining efficacy endpoints (6, 7). These PK/PD endpoints may be more difficult to attain in several frail populations such as the critically ill patients. In fact, due to their severe pathophysiological changes, standard dosing regimens may lead to inadequate concentrations and clinical outcomes. Therefore, implementation of TDM in clinical routine for critically ill patients should be prioritized, especially considering their high mortality rates (8).

In order to better understand aminoglycosides pharmacokinetics and the optimization of drug-administration in critically ill patients, multiple population pharmacokinetic (PopPK) models for gentamicin have been developed throughout the years (9). However, most of them do not include external evaluation during model development. External evaluation, considered as one of the most robust validation methods, consists of using an independent population within the final model to assess the accuracy and reproducibility of predicting antimicrobial concentrations (10). Moreover, PopPK models may also be used to assess the probability of PK/PD target attainment (PTA) with the help simulations based on various drug dosing regimens.

The aim of this study is to externally evaluate published gentamicin PopPK models with a population of ICU patients and to determine their predictive performances.

2. Methods

2.1 Patients

Medical records of adult ICU patients admitted to the Hôpital Sacré-Coeur de Montréal (HSCM) between 2009 and 2019 or the Institut Universitaire de Cardiologie et Pneumologie de Québec (IUCPQ) between 2014 and 2020 and who received at least one dose of gentamicin and one serum concentration were retrospectively reviewed. Ethical approval was obtained from the Comité d'Éthique du CIUSSS-du-Nord-de-l'Île-de-Montréal (MP-32-2020-1904) and the Comité d'Éthique de la Recherche Clinique de l'Université de Montréal (#CERC-19-073-R).

Data extraction from the medical records included age, sex, serum creatinine, body weight, gentamicin dose administered, gentamicin serum concentrations, infusion time dates and times of all doses and concentrations, concomitant medications, medical history, and admission diagnoses. Creatinine clearance based on Cockcroft-Gault (CL_{CG}) and estimation of glomerular filtration rate (eGFR) were estimated based on the closest time of serum creatinine measurement according to the respective equations (11, 12):

$$eGFR\ \left(\frac{mL}{min}\right) = 186.3\ \times\ (\frac{Scr}{88.4})^{-1.154}\ \times Age^{-0.203} \times (1.212\ if\ black)\ \times (0.742\ if\ female)$$

$$CrCL\ \left(\frac{mL}{\min}\right) = \frac{(140 - Age) \times Bodyweight\ (kg) \times 1.23\ \times (0.85\ if\ female)}{Scr}$$

where Scr is serum creatinine level in µmol/L

2.2 Published models

We previously performed a literature review on aminoglycosides PopPK models in critically ill patients with the following search 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*?))] (9). However, this current study only aims to externally evaluate the gentamicin PopPK models. Moreover, gentamicin PopPK models that were not developed using the nonlinear mixed effect modeling (NONMEM) software were excluded from the external evaluation.

2.3 Model evaluation

External evaluation was conducted with the help of NONMEM® (version 7.5: ICON Development Solutions, Ellicott City, MD, USA), while the plots were designed using R version 4.0.4. The retained PopPK models were described based on the formulas and PK parameters reported from the final model for each publication. No additional fitting was used during the external evaluation (Option in NONMEM was set to MAXEVAL= 0). Moreover, the global fit of the PopPK models was also assessed with goodness-of-fit (GOF) plots of the predicted concentrations *vs* the observed concentrations. Predictive performance of the models was evaluated with prediction error (PE) determined by the following equation:

$$PE\ (\%) = \frac{C_{pred,i} - C_{obs,i}}{C_{obs,i}} \times 100\%$$

Where C_{pred} and C_{obs} corresponds to the *i*th predicted concentration by the model and the observed concentration, respectively (13) Moreover, in order to quantify bias and inaccuracy, median prediction error (MDPE) and median absolute prediction error (MADPE) were used with the following equations:

1) Bias : $MDPE_i(\%) = median\ (PE_{ij}, j = 1, \dots, N_i$
2) Inacurracy : $MADPE_i(\%) = median\ (|PE_{ij}|, j = 1, \dots, N_i$

In order to considered unbiased, MDPE should be between -20 and 20%, whereas to be considered accurate, MADPE value should be ≤ 30% (14). Finally, normalized prediction distribution error (NPDE) analysis was also a strategy used in order to establish the overall fit of the PopPK model with the independent databases.

2.4 Evaluations of C_{max} and C_{min} following 3rd dose

Considering that gentamicin's clinical efficacy, as well as the other aminoglycosides, is based on C_{max}/MIC, the prediction of C_{max} concentration following the third dose was assessed ($C_{max,3rd}$)

with different dosing regimens. Moreover, pre-dose concentration (C_{min}) before the 4th was also examined. These simulated PK/PD endpoints were to be done based on the patients' covariates only (*a priori* prediction). The evaluation of these simulated concentrations was only completed with the best performing PopPK model in terms of overall predictive performance (GOF plots, MDPE and MADPE).

3. Results

Medical records of 48 and 39 ICU patients from IUCPQ and HSCM were recruited for this study, respectively. Table 1 describes the demographic characteristics of both populations, separately and altogether. The only demographic characteristics that were statistically different between both institutions were the repartition of genders and the creatinine serum values (SCr). Moreover, total daily dose in HSCM appeared to be somewhat higher and more variable than in IUCPQ. In fact, IUCPQ mostly generalizes their care towards people with cardiopulmonary diseases, therefore the vast majority of the patients from IUCPQ included in this study suffered from endocarditis. Whereas HSCM's patients suffered a variety of conditions mostly leading to sepsis.

Table 1: Demographic characteristics of the patients in the evaluated models and the external validation datasets

Characteristics	Rea (15)	Bos (16)	Hodiamont (17)	Hodiamont (18)	HSCM	IUCPQ	Combined
Number of patients (N)	102	48	42	59	39	48	87
M/F	45/57	24/24	20/22	29/30	18/21	36/12	54/33
Age (years)	61.4 ± 16.4	40.0 (20-86)	61.0 (20-78)	60.9 ± 17.2	60.3 ± 19.2	58.7 ± 16.9	59.4 ± 17.9
Weight (kg)	81.4 ± 30.3	51.0 (33-76)	70.5 (42.0-116)	79.2 ± 22.0	79.4 ± 20.5	80.5 ± 22.4	80.0 ± 21.5
Serum creatinine (µmol/L)	194.5 ± 168	76.0 (37-1192)	115.0 (36-1719)	-	93.2 ± 91.4	99.9 ± 34.8	96.9 ± 66.0
CrCl (mL/min)	-	74.0 (4 – 155)	54.9 (4.0-150)	-	99.8 ± 60.6	86.0 ± 36.4	92.2 ± 48.9
Total daily dose (mg/kg)					2.9 ± 0.9	2.0 ± 0.7	2.4 ± 1.1

The values are presented as median (range) or mean ± SD. *HSCM:* Hôpital du Sacré-Cœur de Montréal, *IUCPQ :* Institut Universitaire de Cardiologie et Pneumologie de Québec, *M/F* : Male/Female, *CrCl* : Creatinine clearance, *Combined* : Combined datasets from HSCM and IUCPQ

As per gentamicin's PopPK models in Duong et al. literature review, eleven models were screened (9). Amongst them, seven were excluded due to lack of information or the models were not developed with NONMEM. Therefore, the predictive performance was evaluated for four models (15-18). Demographic characteristics are presented in Table 1. Pharmacokinetic equations of the four evaluated models are presented in Table 2. Half of them used mono-compartment model, whereas the other half used bi-compartment model. Covariates used were varied with Glomerular filtration (n=1), CrCL (n=1), covariates related to weight (n=2), albumin (n=1). Gentamicin CL and total volume of distribution ranged between 1.15 to 5.7 L/h and 19 to 54 L.

Table 2: Summary of the characteristics of the evaluated PopPK models

Model	Cmpt	Cov	Error	CL	IIV_{CL} (%)	V or V_1	IIV_V or V1 (%)	Q	IIV_Q (%)	V_2	IIV_{V2} (%)	Residual variability		Model equations
												Proportional (%)	Additive (mg/L)	
Rea RS et al. (15)	1	GFR, BW	Mixed	3.14	83.7	53	64.4	-	-	-	-	24.3	0.381	$CL = (3.14 \times GFR^{1.2}) / (54.8 + GFR^{1.2})$ $V_1 = 53 \times (BW/70)$
Bos JC et al.(16)	1	CrCl	Mixed	5.7	74	19	49	-	-	-	-	32	0.056	$CL = 5.7 \times (1 + 0.0091 \times (CrCl - 74)$
Hodiamont et al.(17)	2	IBW, ALBM	Proportional	1.15	42.5	21.2	17.2	1.96	-	18.4	-	-	-	$CL = 1.15 \times (IBW/70)^{0.75}$ $V_1 = 21.2 \times (IBW/70) \times (ALBM/22)^{-0.833}$
Hodiamont et al. (18)	2	-	Mixed	2.3	75.0	21.6	27.0	1.3	-	10.2	-	19.4	0.13	-

Cmpt, compartment; *Cov*, covariates, *CL,* clearance; *V*, central volume of distribution; V_1, volume of distribution of the first compartment; *Q*, inter-compartmental clearance; V_2, volume of distribution of the second compartment; *IIV,* interindividual variability, *ALBM,* Albumin, *CrCl*, creatinine clearance; *GFR*, glomerular filtration rate, *BW,* bodyweight, *IBW*, ideal bodyweight.

The results presented in this article are from the external evaluation with the combined datasets from HSCM and IUCPQ. Results from the additional external evaluations with the separate datasets are presented in the *Supplementary Information.* Population-predicted versus observed concentrations are presented in Figure 1 for each evaluated model. The models from Bos et al. and Hodiamont et al. appeared to over-predict the observed concentrations (16, 18), while models from Rea et al. and Hodiamont et al. tend to underpredict the observed concentrations from the validated dataset (15, 17). Following external evaluation, bias and imprecision values ranged between -18.02 to 10.56% and 18.86 to 27.06%, respectively.

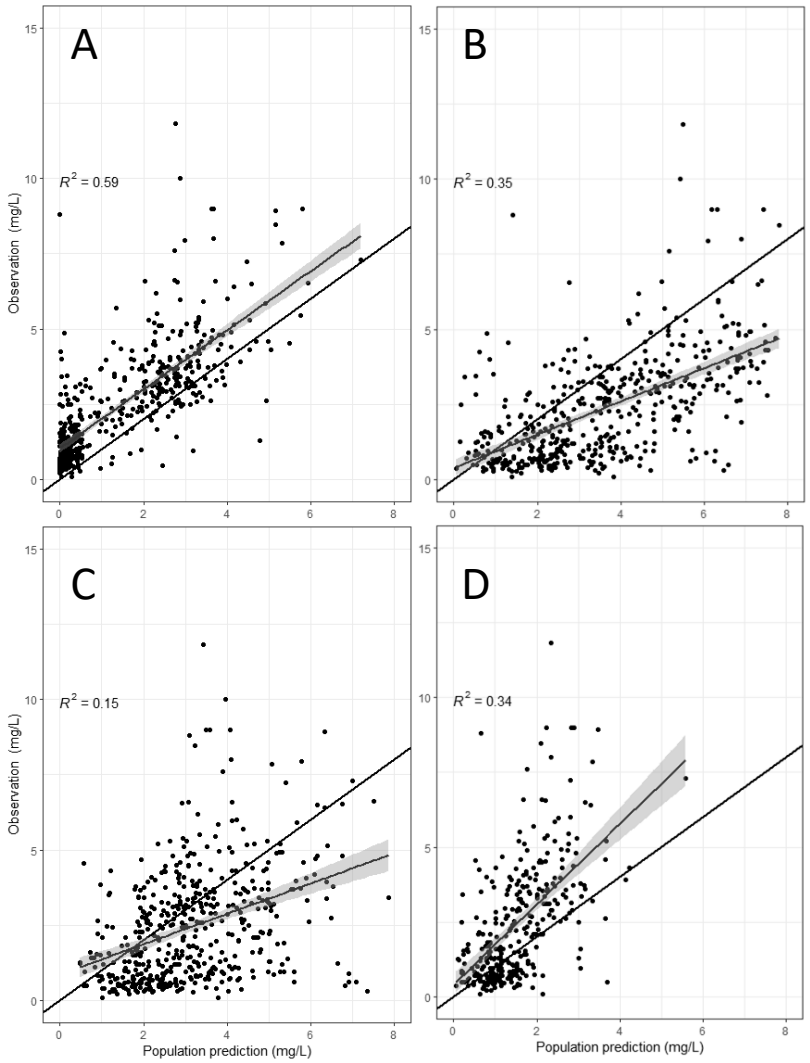

Figure 1 : Population-predicted concentration *versus* observed concentrations for gentamicin models. **A.** Bos et al. (16), **B.** Rea et al. (15), **C.** Hodiamont et al. (17), **D.** Hodiamont et al. (18). Black line with shaded area represents the trendline from the scatter points.

As per presented in Table 3, although all four evaluated models respected the targeted ranges for bias (±20%) and imprecision (≤ 30%) (14), only the model from Bos et al. was able adequately predict the observed concentrations, based on Figure 1. Table S1 from the *Supplementary Information* presents the bias and imprecision values for each institution separately. Since model from Bos et al. was considered the best performing model, it was used for therapeutic target simulations. Both therapeutic targets ($C_{max,\ 3rd\ dose}$ and predose before the 4th administration) were simulated for several dosing regimens (MDD and ODD) in the combined datasets of HSCM and IUCPQ. Moreover, Table S2 from the *Supplementary Information* presents the statistical results

performed during the Normalized Prediction Distribution Errors (NPDE). Based on the different statistical tests performed (Student's t-test, Fischer variance test and Shapiro-Wilk test), the normality of the NPDE distribution was generally not established.

Table 3 Prediction error following external evaluation of the PopPK models

Model	MDPE (%)	MADPE (%)
Rea RS et al. (15)	-18.02	27.06
Bos JC et al.(16)	-4.54	18.86
Hodiamont et al.(17)	10.56	23.22
Hodiamont et al. (18)	-14.73	24.57

MDPE, median prediction error; *MADPE*, median absolute prediction error

Simulations were based on two different efficacy targets: C_{maz}/MIC > 8 and C_{maz}/MIC > 10. Figure 2 presents the probability of target attainment (PTA) based on the MIC values and the dosing regimen used. Moreover, Table 4 presents the same PTA but displayed by total dose give per day for C_{max}/MIC > 10, while Table 5 displays PTA for pre-dose concentrations before the 4^{th} administration for C_{max}/MIC > 10. PTA results based on for C_{max}/MIC > 8 are presented in Table S3 of the *Supplementary Information*. For each of the 5 simulated doses given per day (3 to 7 mg/kg/day), the once-daily-dosing regimen was the best dosage in order to maximizes the probability of target attainment, for all MIC values, as compared to the multiple-daily-dosing regiment (twice or thrice daily). Similarly, for the pre-dose concentrations, ODD had a higher probability of respecting toxicity targets as compared to the MDD (twice or thrice daily).

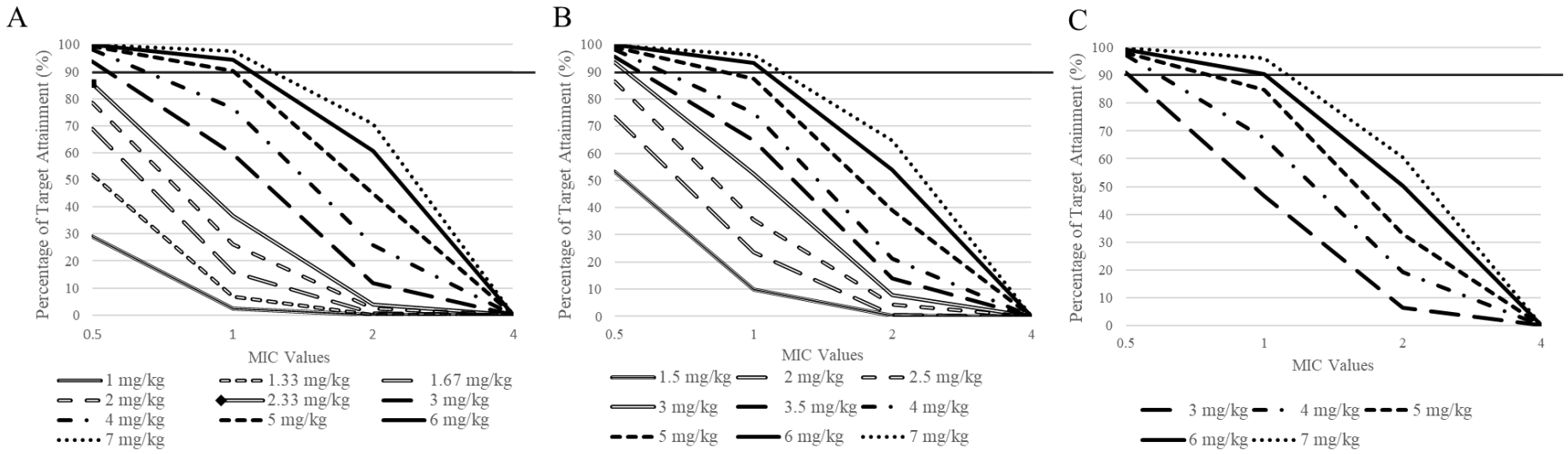

Figure 2 : Probability of target attainment of C_{max}/MIC >10 on the 3rd dose based on different MIC Values. **A.** Dose administered thrice daily (every 8 hours), **B.** Dose administered twice daily (every 12 hours), **C.** Dose administered daily (every 24 hours)

Table 4: Probability of target attainment of C_{max}/MIC >10 on the 3rd dose based on different MIC values and MDD and ODD dosing regimens of gentamicin

	3 mg/kg per day (%)			4 mg/kg/day (%)			5 mg/kg/day (%)			6 mg/kg per day (%)			7 mg/kg/day (%)		
MIC	1 mg/kg/q8h	1.5 mg/kg/q12h	3 mg/kg/q24h	2 mg/kg/q8h	3mg/kg/q12h	4 mg/kg/q24h	1.67 mg/kg/q8h	2.5 mg/kg/q12h	5 mg/kg/q24h	2 mg/kg/q8h	3mg/kg/q12h	6 mg/kg/q24h	2.33 mg/kg/q8h	3.5 mg/kg/q12h	7 mg/kg/q24h
0.5	29.1	53.4	91.1	78.7	93.4	97.3	68.9	86.6	98.3	78.7	93.4	99.2	85.7	95.6	99.9
1	2.4	9.9	46.6	26.1	52.4	67.4	16	35.6	84.7	26.1	52.4	90.4	36.6	64.7	96.2
2	0.1	0.4	6.3	2.4	7.9	19.3	0.8	4.2	32.9	2.4	7.9	50.2	3.9	14.1	60.6
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

MIC, Minimum inhibitory concentration; *q8h,* every 8 hours; *q12h,* every 12 hours, *q24h*, every 24 hours

Table 5: Probability of target attainment of pre-dose concentration (C_{min}) before the 4th dose based on different dosing regimens (MDD and ODD) of gentamicin

	3 mg/kg per day (%)			4 mg/kg/day (%)			5 mg/kg/day (%)			6 mg/kg per day (%)			7 mg/kg/day (%)		
C_{min} (mg/L)	1 mg/kg/q8h	1.5 mg/kg/q12h	3 mg/kg/q24h	1.33 mg/kg/q8h	2 mg/kg/q12h	4 mg/kg/q24h	1.67 mg/kg/q8h	2.5 mg/kg/q12h	5 mg/kg/q24h	2 mg/kg/q8h	3mg/kg/q12h	6 mg/kg/q24h	2.33 mg/kg/q8h	3.5 mg/kg/q12h	7 mg/kg/q24h
<1	66.7	72.3	86.7	62.2	69.5	72.8	55	65.3	82.6	52.5	66.7	81.1	49.2	60.7	80.1
<0.5	44.9	56.6	70.9	43.1	53.2	52.6	40	48.2	66.2	37.5	48.3	65.5	36.4	45.2	64.9

Cmin, predose concentration; *q8h,* every 8 hours; *q12h,* every 12 hours, *q24h*, every 24 hours

4. Discussion

In the past decades, multiple PopPK models for gentamicin in critically ill patients were developed (9). From the 11 gentamicin models developed in critically ill patients, only one of them performed an external evaluation during their model development process (19). In this current study, following exclusion criteria, the predictive performance of 4 models were evaluated with an independent dataset with medical records from two Quebec institutions (15-18). Model's appropriateness should be evaluated based on an integrative assessment of several markers such as bias, imprecision and GOF plots. Based on bias and imprecision values, all four models were in the determined values, thereby suggesting that all four models would be suitable for clinical application. However, based on the observed *vs* predicted concentrations from the models, only the model from Bos et al.(16) appeared to slightly underpredict gentamicin concentrations (16). The other three models showed greater under- or overprediction of the observed gentamicin concentrations. Underprediction and overprediction of actual therapeutic drug monitoring concentrations may result in a misinterpretation of efficacy and toxicity targets, respectively. Moreover, results from NPDE simulations are often considered as an indicator of the accuracy from the model. Based on the results of non-normality of the distribution errors for all four models with all three validation datasets (HSCM, IUCPQ and combined), usage of this models in clinical settings should be done cautiously.

Our external validation datasets formed with two Quebec institutions consisted of patients with severe infections or endocarditis which was comparable to the populations used to develop the evaluated models (15-18). Although the four evaluated models respected the bias and imprecision values, variability remains in the prediction of the actual gentamicin concentrations. This variability could have been caused by several sources such as the severity of the illness, medical history, and its related concomitant medication. Moreover, variability may also be caused by these differences between patients of the developed PopPK model. In fact, as shown in Table 2, interindividual and residual variabilities for PK parameters were already high, thereby suggesting that the patients, from the original dataset used in model development, were different from each other. One model included creatinine clearance based on the Cockcroft-Gault equation (CL_{CG}) (16). Since the latter equation includes other variables such as age, bodyweight and sex, these

variables were also taken into account in the estimation of gentamicin clearance. Rea et al. used glomerular filtration rate as a covariate for gentamicin CL instead of $CL_{CG.}$ The best estimator for gentamicin is still up to debate. Zarowitz et al. established that GFR represents a better indicator for the estimation of gentamicin CL (20), where as Lim et al. determined that GFR calculated by CKD-EPI adjusted by body surface area would be the most accurate one (21). Covariates related to BW were included in two studies (15, 17). Since dose optimization may be affected by BW, its inclusion in the relation with volume of distribution is expected (22).

Also, variability seen during the external evaluation may also be due to the different study designs from the developed PopPK models. In fact, the number of patients in the validation dataset was greater than most study populations used for model development (16-18). Moreover, three studies had similar sampling schedule to the validation datasets with samples from therapeutic drug monitoring (15, 17, 18). Whereas the model from Bos et al. (16) was developed with samples collected following a prospective observational design. Alihodzic et al. demonstrated that erroneous records due to clinical routine practices may lead to inaccurate estimation of PK parameters during PopPK model development (23). Furthermore, variability may also be due to the origin of the study populations of the developed models. These models were either developed based on critically ill patients from United States, Africa, or Europe.

For the evaluations of C_{max} and C_{min} following the 3rd gentamicin administration, the ODD regimen appeared to be the best option in order to maximizes the PTA of efficacy (C_{max}/MIC > 10) and toxicity (C_{min} < 1 mg/L or C_{min} < 0.5 mg/L) targets compared to the MDD regimen. This finding is consistent with previous literature stating that ODD regimens were able to maintain efficacy while minimizing signs of toxicity (6, 7). Although ODD appears to be the better choice between twice and thrice daily, only total daily dose of 3, 4 and 5 mg/kg had a PTA greater than 90% for MIC value of 0.5 mg/L. In fact, as per latest MIC breakpoints from United States Committee on Antimicrobial Susceptibility Testing (USCAST) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), *Staphylococcus spp, Pseudomonas spp* and *Enterococcus spp.* present MIC value ranging from 1 to 2 mg/L. Considering these actual MIC values, only 6 and 7 mg/kg/day have a greater PTA of 90% for MIC value of 1 mg/L, while none of the simulated dosing regimens would respect the 90% PTA for MIC value of 2 mg/L. In fact, Bos et al. also performed similar dosing regimen simulations with a therapeutic target of C_{max}/MIC > 8 (16).

Several limitations should be considered in this current study. Firstly, concentrations from the medical records from both institutions were therapeutic drug monitoring data collected during a clinical setting. Therefore, number of samples per patient were limited. Moreover, considering that we chose the NONMEM software as an inclusion criterion may have restricted the number of models to be evaluated.

5. Conclusion

In conclusion, the predictive performance of the evaluated gentamicin PopPK models developed in critically ill patients was adequate with two independent populations of critically ill patients from Quebec. Although, the predictive performance was within acceptable ranges of bias and imprecision, variability still remains and may cause under- or overprediction of gentamicin concentrations depending on the model used. With the best performing model from Bos et al., dosing regimens were simulated with our study population. Based on our results, we confirmed Bos et al.'s recommendation of an ODD of 6 to 7 mg/kg/day in order to maximize therapeutic targets of C_{max}/MIC >8 or C_{max}/MIC>10, considering MIC value of 1 mg/L. However, with these optimal dosing regimens, toxicity targets should still be monitored closely, as gentamicin accumulation may occur, especially in patients with impaired renal function. Adjustment of subsequent doses must be performed cautiously, following confirmation of MIC values of pathogens, to ensure clinical efficacy.

6. References

1. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: An Overview. Cold Spring Harb Perspect Med. 2016;6(6):a027029.
2. Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM. Aminoglycosides: activity and resistance. Antimicrobial agents and chemotherapy. 1999;43(4):727-37.
3. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am. 2009;23(4):791-vii.
4. Alfred S.Gin RA, Sheryl Zelenitsky, Murray Ducharme, Keith A.Rodvold, George A.Zhanel. The practice of once-daily aminoglycoside dosing in Canada: A national survey. Can J Hosp Pharm. 1999;52:12-7.
5. Chuck SK, Raber SR, Rodvold KA, Areff D. National Survey of Extended-Interval Aminoglycoside Dosing. Clinical Infectious Diseases. 2000;30(3):433-9.
6. Barclay ML, Kirkpatrick CMJ, Begg EJ. Once Daily Aminoglycoside Therapy. Clinical Pharmacokinetics. 1999;36(2):89-98.
7. Stankowicz MS, Ibrahim J, Brown DL. Once-daily aminoglycoside dosing: An update on current literature. American Journal of Health-System Pharmacy. 2015;72(16):1357-64.
8. Tängdén T, Ramos Martín V, Felton TW, Nielsen EI, Marchand S, Brüggemann RJ, et al. The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections. Intensive Care Medicine. 2017;43(7):1021-32.
9. Duong A, Simard C, Wang YL, Williamson D, Marsot A. Aminoglycosides in the Intensive Care Unit: What Is New in Population PK Modeling? Antibiotics. 2021;10(5).
10. Brendel K, Comets E, Laffont C, Mentré F. Evaluation of different tests based on observations for external model evaluation of population analyses. Journal of Pharmacokinetics and Pharmacodynamics. 2010;37(1):49-65.
11. Manjunath G, Sarnak MJ, Levey AS. Estimating the glomerular filtration rate. Postgraduate Medicine. 2001;110(6):55-62.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
13. Guang W, Baraldo M, Furlanut M. Calculating percentage prediction error: A user's note. Pharmacological Research. 1995;32(4):241-8.
14. Hara M, Masui K, Eleveld DJ, Struys MMRF, Uchida O. Predictive performance of eleven pharmacokinetic models for propofol infusion in children for long-duration anaesthesia. British Journal of Anaesthesia. 2017;118(3):415-23.
15. Rea RS, Capitano B, Bies R, Bigos KL, Smith R, Lee H. Suboptimal aminoglycoside dosing in critically ill patients. Ther Drug Monit. 2008;30(6):674-81.
16. Bos Jeannet C, Prins Jan M, Mistício Mabor C, Nunguiane G, Lang Cláudia N, Beirão José C, et al. Population Pharmacokinetics with Monte Carlo Simulations of Gentamicin in a Population of Severely Ill Adult Patients from Sub-Saharan Africa. Antimicrob Agents Chemother.63(4):e02328-18.
17. Hodiamont CJ, Juffermans NP, Bouman CSC, de Jong MD, Mathôt RAA, van Hest RM. Determinants of gentamicin concentrations in critically ill patients: a population pharmacokinetic analysis. International Journal of Antimicrobial Agents. 2017;49(2):204-11.
18. Hodiamont CJ, Janssen JM, de Jong MD, Mathôt RA, Juffermans NP, van Hest RM. Therapeutic Drug Monitoring of Gentamicin Peak Concentrations in Critically Ill Patients. Therapeutic Drug Monitoring. 2017;39(5).

19. Gomes A, van der Wijk L, Proost JH, Sinha B, Touw DJ. Pharmacokinetic modeling of gentamicin in treatment of infective endocarditis: Model development and validation of existing models. PLoS One. 2017;12(5):e0177324-e.
20. Zarowitz BJ, Robert S, Peterson EL. Prediction of Glomerular Filtration Rate Using Aminoglycoside Clearance in Critically Ill Medical Patients. Annals of Pharmacotherapy. 1992;26(10):1205-10.
21. Lim AKH, Mathanasenarajah G, Larmour I. Assessment of aminoglycoside dosing and estimated glomerular filtration rate in determining gentamicin and tobramycin area under the curve and clearance. Internal Medicine Journal. 2015;45(3):319-29.
22. Marsot A, Guilhaumou R, Riff C, Blin O. Amikacin in Critically Ill Patients: A Review of Population Pharmacokinetic Studies. Clinical Pharmacokinetics. 2017;56(2):127-38.
23. Alihodzic D, Broeker A, Baehr M, Kluge S, Langebrake C, Wicha SG. Impact of Inaccurate Documentation of Sampling and Infusion Time in Model-Informed Precision Dosing. 2020;11(172).

7. Supplementary Information

Table *S1:* Prediction error following external evaluation of the PopPK models for each institution separately

	HSCM only		IUCPQ only	
Model	MDPE (%)	MADPE (%)	MDPE (%)	MADPE (%)
Rea RS et al. (15)	-20.09	26.16	-18.36	27.32
Bos JC et al.(16)	-4.62	12.97	-4.30	20.90
Hodiamont et al.(17)	5.50	18.85	14.96	26.23
Hodiamont et al. (18)	-17.35	25.59	-14.65	24.48

HSCM, Hôpital Sacré-Coeur de Montréal; *IUCPQ,* Institut Universitaire de Cardiologie et Pneumologie de Québec, *MDPE,* median prediction error; *MADPE*, median absolute prediction error

Table *S2:* Normalized-Prediction Distribution Error (NPDE)

	Rea RS et al. (15)			Bos JC et al.(16)			Hodiamont et al. (17)			Hodiamont et al. (18)		
	HSCM	IUCPQ	Combined	HSCM	IUCPQ	Combined	HSCM	IUCPQ	Combined	HSCM	IUCPQ	Combined
T-Test	OK	OK	OK	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.05	P<0.001
Fisher	P<0.001	P<0.001	P<0.001	P<0.001	OK	OK	OK	P<0.01	P<0.05	P<0.001	P<0.001	P<0.001
SW-Test	OK	OK	OK	OK	P<0.001	P<0.001	P<0.05	P<0.001	P<0.001	OK	P<0.01	P<0.05

HSCM, Hôpital Sacré-Coeur de Montréal; *IUCPQ,* Institut Universitaire de Cardiologie et Pneumologie de Québec, *Combined* : Combined datasets from HSCM and IUCPQ, *SW* : Shapiro-Wilk Test of Normality

Table *S3 :* Probability of target attainment of C_{max}/MIC >8 on the 3rd dose based on different MIC values and MDD and ODD dosing regimens of gentamicin

	3 mg/kg per day (%)			4 mg/kg/day (%)			5 mg/kg/day (%)			6 mg/kg per day (%)			7 mg/kg/day (%)		
MIC	1 mg/kg/q8h	1.5 mg/kg/q12h	3 mg/kg/q24h	1.33 mg/kg/q8h	2.33 mg/kg/q8h	2.33 mg/kg/q8h	2.33 mg/kg/q8h	2.5 mg/kg/q12h	5 mg/kg/q24h	2 mg/kg/q8h	3mg/kg/q12h	6 mg/kg/q24h	2.33 mg/kg/q8h	3.5 mg/kg/q12h	7 mg/kg/q24h
0.5	46	70.5	94.9	66.9	85.4	98.8	81.6	93	99.5	88	96.2	99.8	92.7	98.6	100
1	5.7	18.5	62.8	16.2	36.3	82.5	30.5	57.4	91.2	45.4	70.6	94.7	54.5	80.2	98
2	0.3	1.3	14.5	0.6	4	32.6	3.2	10.5	50	5.4	17.6	66.2	11.3	28.1	76
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

MIC, Minimum inhibitory concentration; *q8h,* every 8 hours; *q12h,* every 12 hours, *q24h*, every 24 hours

CHAPITRE 5 – DISCUSSION

Ce projet a permis la description des pratiques habitudes de posologies et de suivi thérapeutique spécifiquement chez les patients hospitalisés en unités de soins intensifs dans les établissements de santé dans la province du Québec, une revue de la littérature des modèles PopPK d'aminosides (amikacine, gentamicine et tobramycine) et une évaluation externe de la performance prédictive des modèles de gentamicine avec une population de patients québécois.

La famille des aminosides est un exemple d'anti-infectieux, parmi tant d'autres, pour laquelle les pratiques d'adaptation et de suivis thérapeutiques pourraient être améliorées. En effet, sa grande variabilité inter- et intra-individuelle combinée aux risques de toxicités réversibles et irréversibles constituent un défi de taille pour les cliniciens afin d'assurer une efficacité clinique, notamment auprès des patients aux soins intensifs.

Le volet 1 de ce projet est le premier questionnaire sur les pratiques habituelles des aminosides depuis les 20 dernières années et le premier questionnaire visant spécifiquement les patients aux soins intensifs. Au fil des années, une transition graduelle d'une administration multiple par jour vers une administration uniquotidienne a été remarquée. Le questionnaire de Gin et al., développé en 1999 visant les établissements de santé au Canada, a démontré que 40% des répondants n'utiliseraient pas l'administration uniquotidienne(15). Près de 20 ans plus tard, au Québec, les résultats du volet 1 ont démontré que seulement 6% des répondants affirment ne pas utiliser l'administration uniquotidienne. Comparativement aux États-Unis, un questionnaire semblable a été effectué en 1998 où près de trois établissements sur quatre utilisaient déjà l'administration uniquotidienne pour des régimes posologiques de plus de 5 mg/kg. De plus, les établissements de santé américains, comparativement aux établissements canadiens et québécois, semblent davantage utiliser l'amikacine dans leur traitement contre des infections de type Gram-négatif. En effet, l'amikacine est peu administrée, comparativement à la gentamicine et la tobramycine, pour des infections graves dans les établissements du Québec. Étant donné le peu d'établissements utilisant l'amikacine (21% des répondants), les pratiques de posologies et de suivi thérapeutique n'ont pas pu être adéquatement représentées. Concernant les doses utilisées de gentamicine et de tobramycine, 70% des répondants utilisent une dose uniquotidienne de 5 à 7 mg/kg et la dose multiquotidienne la plus utilisée est 1.7 mg/kg à chaque 8 heures. Ces dernières respectent les

recommandations et monographies des différentes agences européennes, américaines et australiennes (11, 35, 36).

Pour la gentamicine et la tobramycine, les cibles thérapeutiques d'efficacité (C_{max}/CMI >8 ou >10) et de toxicité (C_{min} < 0.5 mg/L – 2 mg/L) utilisées par les cliniciens au Québec sont généralement cohérentes avec les recommandations de la littérature et avec les valeurs de CMI établies par l'EUCAST et l'USCAST (8, 9). Il est important de mentionner que quelques répondants sembleraient utiliser des cibles d'efficacité plus élevées que nécessaires. Ainsi, une uniformisation des pratiques de suivi thérapeutique serait nécessaire à travers la province. Au niveau de l'adaptation posologique, environ un répondant sur trois utiliseraient leur jugement clinique (33%) ou un outil de calcul maison (27%) dans des situations où les concentrations posologiques ne reflètent pas les cibles thérapeutiques attendues. En sachant que les patients aux soins intensifs présentent des changements physiopathologiques influençant la pharmacocinétique des aminosides, un intérêt grandissant se manifeste au niveau de ces outils de calcul, tels que le *model-informed precision dosing* (MIPD), permettant d'ajuster les doses subséquentes en fonction des caractéristiques de chaque patient (37). Les MIPDs, une forme de médecine personnalisée, sont basés sur l'utilisation de modèles pharmacocinétiques de population combinée avec l'inférence bayésienne afin d'optimiser la guérison clinique (37).

Au fil des dernières années, plusieurs de ces modèles PopPK ont été développées pour les aminosides chez les patients hospitalisés en unités de soins intensifs. Le volet 2 de ce projet a permis de décrire les caractéristiques des modèles PopPK de l'amikacine, la gentamicine et la tobramycine. La pharmacocinétique de la tobramycine et de l'amikacine étaient généralement mieux décrites par des modèles bi-compartimentaux, tandis que la pharmacocinétique de la gentamicine était majoritairement décrite par des modèles mono-compartimentaux. En revanche, il est nécessaire de noter que le design de l'étude ainsi que la qualité des prélèvements sanguins peuvent affecter la structure du modèle et l'estimation des paramètres PK. En effet, les études ayant des concentrations de suivi thérapeutique ou des temps de prélèvements sanguins éparses (*sparse sampling*) étaient associés à des modèles mono-compartimentaux (n=8). Plusieurs covariables ont été testées à travers les 19 modèles, mais seulement certaines covariables ont été retenues dans le modèle afin de mieux décrire les paramètres PK. Par exemple, la clairance à la créatinine calculée avec l'équation de Cockcroft-Gault était incluse dans huit modèles afin de mieux décrire la

clairance des aminosides. Les covariables reliées au poids ou à la taille corporelle ont été incluses dans cinq modèles afin de mieux décrire le volume de distribution des aminosides. Les valeurs médianes de clairance et de volume de distribution étaient similaires entres-elles, mais les paramètres PK étaient toutefois variables d'un modèle à l'autre pour une même molécule. Cette variabilité pourrait être causée par les différentes comorbidités additionnelles retrouvées dans les populations à l'étude, telles que la dysfonction cardiaque, le sepsis, la dysfonction rénale et même de l'hyperclairance rénale.

Bien que 19 modèles aient été développés pour ces trois aminosides, seulement trois études ont effectué une évaluation externe avec une base de données indépendantes. Malgré que l'évaluation externe soit considérée comme la méthode la plus robuste, cette dernière n'est pas fréquemment appliquée (38). En effet, ce manque d'évaluation externe pourrait être due à la difficulté de récolter des données d'un nombre suffisant de patients ayant des caractéristiques similaires à notre population initiale dans un autre établissement. De plus, malgré des résultats positifs suivant l'évaluation, cette dernière n'assure pas la transférabilité du modèle à toutes les populations confondues. En effet, la performance prédictive établie durant l'évaluation externe est souvent connue d'obtenir des valeurs de biais et d'imprécision inadéquates, notamment pour les populations aux soins intensifs ou autres populations spéciales démontrant de la grande variabilité (39-40).

Étant donné le nombre élevé de modèles PopPK d'aminosides développés pour les patients aux soins intensifs dans la littérature, le volet 3 de ce projet consistait à déterminer si ces modèles seraient adaptés à la population québécoise aux soins intensifs.

Un nombre suffisant de données-patients ont été collectées pour la gentamicine et la tobramycine à l'Hôpital Sacré-Cœur de Montréal (HSCM) et l'Institut Universitaire de Cardiologie et Pneumologie de Québec (IUCPQ). Tel qu'attendu en fonction des résultats du questionnaire dans le volet 1 de ce projet, très peu de patients ont reçu de l'amikacine dans ces deux établissements. Ainsi, l'évaluation externe des modèles de gentamicine a été effectuée pour quatre modèles. Bien que l'ensemble de ces quatre modèles ait respecté les critères des biais et d'imprécision, ces derniers avaient tendance à sous- ou surestimer les concentrations observées. Ces estimations inexactes des concentrations du suivi thérapeutique posologique peuvent impliquer une interprétation erronée de l'atteinte des cibles d'efficacité et/ou de toxicité. Avec les données de

tobramycine et en suivant une méthodologie similaire, une évaluation externe des modèles de tobramycine est présentement en cours et des résultats préliminaires sont présentés au prochain chapitre.

La variabilité au niveau de la performance prédictive des modèles de gentamicine pourrait être expliquée par les différences caractéristiques démographiques, entre les patients des deux établissements du Québec ainsi que les populations utilisées pour développer les modèles. De plus, la provenance des populations était très variée, avec des patients américains, africains et européens pour les modèles de Rea et al., Bos et al. et les deux modèles d'Hodiamont et al., respectivement (41-43). Considérant que le modèle de Bos et al. a montré une meilleure performance prédictive en termes de valeurs de biais et d'imprécision et au niveau des graphiques de *Goodness of Fit* (GOF), ce dernier a été sélectionné afin de simuler des régimes posologiques en fonction de cibles PK/PD.

Les simulations des régimes posologiques ont démontré que l'administration uniquotidienne permettait une plus grande atteinte des cibles de C_{max}/CMI >8 et C_{max}/CMI >10 ainsi que des valeurs de concentrations pré-doses sécuritaires. Ce résultat est cohérent avec les résultats du volet 1 où une transition de l'administration multiquotidienne vers l'administration uniquotidienne avait été remarquée dans les établissements de santé. Une administration uniquotidienne de 6 à 7 mg/kg permettrait de maximiser la probabilité d'atteindre les cibles thérapeutiques de C_{max}/CMI >10 en considérant une valeur de CMI de 1 mg/L, tout en minimisant les risques de toxicité. Ce régime posologique optimal obtenu est cohérent avec les pratiques habituelles de dosage au Québec décrites dans le volet 2 de ce projet. Ce modèle pourrait ainsi être utilisé en clinique en le combinant avec l'inférence bayésienne avec d'effectuer des adaptations posologiques au sein des patients adultes admis aux soins intensifs au Québec. En revanche, son utilisation dans un contexte clinique devrait également se faire avec prudence en raison de la variabilité observée au niveau de la prédiction des concentrations réelles.

CHAPITRE 6 – CONCLUSION

En conclusion, ce projet a démontré que l'utilisation adéquate des anti-infectieux, tels que les aminosides, peut être un grand défi, notamment auprès des populations spéciales comme les patients aux soins intensifs.

Le volet 1 de ce projet, sous la forme d'un questionnaire, a permis de décrire les pratiques habituelles d'administration des aminosides à travers la province ainsi que la nécessité d'uniformiser les cibles thérapeutiques visées par les cliniciens. Ensuite, le volet 2, sous la forme d'une revue de la littérature, a permis de révéler les caractéristiques les plus communes lors du développement des modèles PopPK des aminosides ainsi qu'un manque marqué d'évaluation externe de ces modèles. Finalement, le volet 3 a permis l'évaluation externe des modèles de gentamicine trouvées au volet 2 avec une base de données formée de deux populations provenant de deux établissements de santé au Québec. En fonction du meilleur modèle évalué, un régime posologique *a priori* a pu être simulé permettant d'optimiser l'atteinte des cibles thérapeutiques d'efficacité tout en minimisant les concentrations de toxicité.

Étapes futures

La collecte de données-patients ayant reçu de la tobramycine a également eu lieu auprès des établissements de santé de l'HSCM et l'IUCPQ. L'évaluation externe des modèles de tobramycine inclus dans le volet 2 du projet est présentement en cours. Tableau 1. – représente une version préliminaire des résultats de biais et d'imprécision. En considérant qu'aucun modèle ne présente des valeurs acceptables pour notre population cible, le développement d'un nouveau modèle adapté à notre population serait nécessaire.

Tableau 1. – Performance prédictive suivant l'évaluation externe des modèles PopPK

Modèles PopPK	MDPE (%)	MADPE (%)
Aarons et al.(45)	-43,7	45,4
Conil et al.(46)	-17,3	40,0
Hennig et al.(47)	-23,0	39,3

MDPE, median prediction error; *MADPE*, median absolute prediction error

Applications

L'utilisation de modèles PopPK validés dans des populations spéciales, tels que le modèle de Bos et al pour la gentamicine chez les patients aux soins intensifs, permettrait d'effectuer des adaptations posologiques en temps réel à l'aide des caractéristiques des individus, de la cible et de la pathologie. En effet, cette médecine personnalisée permet la combinaison de la modélisation PK/PD avec des estimations mathématiques bayésiennes afin d'optimiser les traitements pour chaque patient. Cet aspect multidisciplinaire serait un atout et permettrait d'améliorer notre façon de prodiguer les soins auprès des patients québécois.

Les résultats obtenus au cours de ce projet de maîtrise seront, entres-autres, utilisés dans mon projet de doctorat. En effet, ce dernier aura pour but de conceptualiser et mettre en place une phase test, avec l'aide de services cliniques, d'un système expert basé sur des modèles PK/PD par approche de population conçu pour l'adaptation des posologies des anti-infectieux en temps réel dans les populations vulnérables. Cet outil serait en mesure de prendre en compte les facteurs individuels des patients, les informations sur le traitement et les résultats de dosage. Par le fait même, nous souhaitons également intégrer la possibilité d'utiliser des modèles PK/PD provenant de la littérature ou même introduire un modèle PK/PD personnalisé afin de permettre une optimisation des traitements pour chaque patient. À l'aide des bases de données provenant des autres projets du *Laboratoire Suivi Thérapeutique Pharmacologique & Pharmacocinétique* (STP^2), la première phase de ce projet se concentrera sur les molécules suivantes : vancomycine en oncohématologie, gentamicine aux soins intensifs et tobramycine aux soins intensifs et en fibrose kystique.

REFERENCES

1. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: An Overview. Cold Spring Harb Perspect Med. 2016;6(6):a027029.
2. Gonzalez LS, 3rd, Spencer JP. Aminoglycosides: a practical review. Am Fam Physician. 1998;58(8):1811-20.
3. Ahmed S, Sony SA, Chowdhury MB, Ullah MM, Paul S, Hossain T. Retention of antibiotic activity against resistant bacteria harbouring aminoglycoside-N-acetyltransferase enzyme by adjuvants: a combination of in-silico and in-vitro study. Scientific Reports. 2020;10(1):19381.
4. Ramirez MS, Tolmasky ME. Aminoglycoside modifying enzymes. Drug Resist Updat. 2010;13(6):151-71.
5. Simon VK, Mösinger EU, Malerczy V. Pharmacokinetic studies of tobramycin and gentamicin. Antimicrob Agents Chemother. 1973;3(4):445-50.
6. Vogelman B, Craig WA. Kinetics of antimicrobial activity. The Journal of Pediatrics. 1986;108(5, Part 2):835-40.
7. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrobial agents and chemotherapy. 1995;39(3):650-5.
8. (USCAST) TUSCoAST. 2021 USCAST Interpretive Tables. 2021. p. 47.
9. (EUCAST) ECOAST. Clinical breakpoints - breakpoints and guidance 2021.
10. Craig WA. Optimizing Aminoglycoside Use. Critical Care Clinics. 2011;27(1):107-21.
11. Australia GoS. Aminoglycosides: Recommendations for use, dosing and monitoring. 2020.
12. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840-51; quiz 59.
13. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des. 2007;13(1):119-26.
14. Nord-de-l'Île-de-Montréal Cd. Guide pratiques - Pharmacocinétique - Aminosides. In: empirique Gda, editor. 2021.
15. Stankowicz MS, Ibrahim J, Brown DL. Once-daily aminoglycoside dosing: An update on current literature. American Journal of Health-System Pharmacy. 2015;72(16):1357-64.
16. Alfred S.Gin RA, Sheryl Zelenitsky, Murray Ducharme, Keith A.Rodvold, George A.Zhanel. The practice of once-daily aminoglycoside dosing in Canada: A national survey. Can J Hosp Pharm. 1999;52:12-7.
17. Chuck SK, Raber SR, Rodvold KA, Areff D. National Survey of Extended-Interval Aminoglycoside Dosing. Clinical Infectious Diseases. 2000;30(3):433-9.
18. Urban AW, Craig WA. Daily dosage of aminoglycosides. Curr Clin Top Infect Dis. 1997;17:236-55.
19. Tobias P, DeMott J, Varughese C, Gurnani P. 649: APPLICATION OF THE HARTFORD NOMOGRAM IN CRITICALLY ILL PATIENTS: A PHARMACOKINETIC STUDY. Critical Care Medicine. 2019;47(1).
20. Xie F, Wang Y, Peng Y, Cheng Z, Li S. Pharmacokinetic/pharmacodynamic evaluation of tobramycin dosing in critically ill patients: the Hartford nomogram does not fit. The Journal of antimicrobial chemotherapy. 2021.

21. Lee J, Yoon S, Shin D, Han H, An H, Lee J, et al. Predictive performance of gentamicin dosing nomograms. Drug Des Devel Ther. 2014;8:1097-106.
22. Vincent JL, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med. 2014;2(5):380-6.
23. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents. Advanced Drug Delivery Reviews. 2014;77:3-11.
24. Sheiner LB, Rosenberg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm. 1977;5(5):445-79.
25. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2013;2(4):e38-e.
26. Tängdén T, Ramos Martín V, Felton TW, Nielsen EI, Marchand S, Brüggemann RJ, et al. The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections. Intensive Care Medicine. 2017;43(7):1021-32.
27. Comets E, Brendel K, editors. Model evaluation in nonlinear mixed effect models, with applications to pharmacokinetics2010.
28. Marsot A, Guilhaumou R, Riff C, Blin O. Amikacin in Critically Ill Patients: A Review of Population Pharmacokinetic Studies. Clinical Pharmacokinetics. 2017;56(2):127-38.
29. Hara M, Masui K, Eleveld DJ, Struys M, Uchida O. Predictive performance of eleven pharmacokinetic models for propofol infusion in children for long-duration anaesthesia. Br J Anaesth. 2017;118(3):415-23.
30. Glass PS, Shafer S, Reves JG. Intravenous drug delivery systems. Miller's Anesth. Philadelphia: Elsevier; 2004. pp. 439–80.
31. Wang YL, Guilhaumou R, Blin O, Velly L, Marsot A. External evaluation of population pharmacokinetic models for continuous administration of meropenem in critically ill adult patients. European Journal of Clinical Pharmacology. 2020;76(9):1281-9.
32. Lv C, Lu J, Jing L, Liu T-T, Chen M, Zhang R, et al. Systematic external evaluation of reported population pharmacokinetic models of vancomycin in Chinese children and adolescents. Journal of Clinical Pharmacy and Therapeutics. 2021;46(3):820-31.
33. Mao JJ, Jiao Z, Yun HY, Zhao CY, Chen HC, Qiu XY, et al. External evaluation of population pharmacokinetic models for ciclosporin in adult renal transplant recipients. Br J Clin Pharmacol. 2018;84(1):153-71.
34. Tasa T, Kalamees R, Vilo J, Lutsar I, Metsvaht T. External evaluation of population pharmacokinetic models for vancomycin in neonates. bioRxiv. 2018:458125.
35. (EMC) EMC. Gentamicin 40mg/ml Injection 2021 [Available from: https://www.medicines.org.uk/emc/product/6531/smpc.
36. (EMC) EMC. Tobramycin 40mg/ml Injection 2021 [Available from: https://www.medicines.org.uk/emc/product/10194/smpc.
37. Darwich AS, Polasek TM, Aronson JK, Ogungbenro K, Wright DFB, Achour B, et al. Model-Informed Precision Dosing: Background, Requirements, Validation, Implementation, and Forward Trajectory of Individualizing Drug Therapy. Annual Review of Pharmacology and Toxicology. 2021;61(1):225-45.

38. Brendel K, Comets E, Laffont C, Mentré F. Evaluation of different tests based on observations for external model evaluation of population analyses. Journal of Pharmacokinetics and Pharmacodynamics. 2010;37(1):49-65.
39. Bukkems LH, Roger C, Hodiamont CJ, Lefrant JY, Juffermans NP, Roberts JA, et al. Predictive performance of a gentamicin population pharmacokinetic model in two western populations of critically ill patients. Int J Antimicrob Agents. 2018;52(2):218-25.
40. Guo T, van Hest RM, Roggeveen LF, Fleuren LM, Thoral PJ, Bosman RJ, et al. External Evaluation of Population Pharmacokinetic Models of Vancomycin in Large Cohorts of Intensive Care Unit Patients. Antimicrobial agents and chemotherapy. 2019;63(5):e02543-18.
41. Rea RS, Capitano B, Bies R, Bigos KL, Smith R, Lee H. Suboptimal Aminoglycoside Dosing in Critically Ill Patients. Therapeutic Drug Monitoring. 2008;30(6).
42. Bos Jeannet C, Prins Jan M, Mistício Mabor C, Nunguiane G, Lang Cláudia N, Beirão José C, et al. Population Pharmacokinetics with Monte Carlo Simulations of Gentamicin in a Population of Severely Ill Adult Patients from Sub-Saharan Africa. Antimicrobial Agents and Chemotherapy.63(4):e02328-18.
43. Hodiamont CJ, Janssen JM, de Jong MD, Mathôt RA, Juffermans NP, van Hest RM. Therapeutic Drug Monitoring of Gentamicin Peak Concentrations in Critically Ill Patients. Therapeutic Drug Monitoring. 2017;39(5).
44. Hodiamont CJ, Juffermans NP, Bouman CSC, de Jong MD, Mathôt RAA, van Hest RM. Determinants of gentamicin concentrations in critically ill patients: a population pharmacokinetic analysis. International Journal of Antimicrobial Agents. 2017;49(2):204-11.
45. Aarons L, Vozeh S, Wenk M, Weiss P, Follath F. Population pharmacokinetics of tobramycin. Br J Clin Pharmacol. 1989;28(3):305-14.
46. Conil JM, Georges B, Ruiz S, Rival T, Seguin T, Cougot P, et al. Tobramycin disposition in ICU patients receiving a once daily regimen: population approach and dosage simulations. Br J Clin Pharmacol. 2011;71(1):61-71.
47. Hennig S, Standing JF, Staatz CE, Thomson AH. Population pharmacokinetics of tobramycin in patients with and without cystic fibrosis. Clin Pharmacokinet. 2013;52(4):289-301.