ABSTRACT: The importance of closely observing patients receiving antibiotic therapy, performing therapeutic drug monitoring (TDM), and regularly adjusting dosing regimens has been extensively demonstrated. Additionally, antibiotic resistance is a contemporary concerningly dangerous issue. Optimizing the use of antibiotics is crucial to ensure treatment efficacy and prevent toxicity caused by overdosing, as well as to combat the prevalence and wide spread of resistant strains. Some antibiotics have been selected and reserved for the treatment of severe infections, including amikacin, gentamicin, tobramycin, and vancomycin. Critically ill patients often require long treatments, hospitalization, and require particular attention regarding TDM and dosing adjustments. As these antibiotics are eliminated by the kidneys, critical deterioration of renal function and toxic effects must be prevented. In this work, clinical data from a Portuguese cohort of 82 inpatients was analyzed and physiologically based pharmacokinetic (PBPK) modeling and simulation was used to study the influence of different therapeutic regimens and parameters as biological sex, body weight, and renal function on the biodistribution and pharmacokinetic (PK) profile of these four antibiotics. Renal function demonstrated the greatest impact on plasma concentration of these antibiotics, and vancomycin had the most considerable accumulation in plasma over time, particularly in patients with impaired renal function. Thus, through a PBPK study, it is possible to understand which pharmacokinetic parameters will have the greatest variation in a given population receiving antibiotic administrations in hospital context.

Keywords: PBPK modeling; therapeutic drug monitoring; antibiotics use; amikacin; gentamicin; tobramycin; vancomycin; GastroPlus™

1. Introduction
Therapeutic drug monitoring (TDM) was implemented in the 1960s to improve patient care and clinical outcome, and specializes in the measurement of circulating drug concentrations to adjust dosing regimens, so as to reach a defined target exposure associated with optimal efficacy and minimal toxicity [1,2]. Since then, some pharmacological properties have been identified (particularly narrow therapeutic window and significant interpatient variability) and the cases that required such dosage individualization have been comprehensively reviewed. TDM is now indicated and recommended for critically ill patients undergoing sufficiently long treatment to justify dosage adjustment [3], whether with
anticancer drugs [4], anti-infectives [5], antiretrovirals [6], biologic therapeutic agents [7] or psychotropic agents [8], etc.

Importantly for this work, therapeutic drug monitoring and dosage adjustments are crucial for antibiotics, and have confirmed beneficial results [9–15]. The four antibiotics studied here, amikacin, gentamicin, tobramycin, and vancomycin, are the most frequently monitored in inpatients, which can be explained by their narrow therapeutic indexes and potential to cause adverse effects, namely nephrotoxicity, particularly in prolonged treatments [15–17]. The value of TDM of these antibiotics has been extensively demonstrated [13,14,18–27].

Furthermore, the increasing resistance rates to antimicrobial agents are a pressing problem that has been indefectibly associated with the inappropriate administration and overuse of these drugs, which has accelerated this process over the past 80 years. About half of the antimicrobial agents prescribed to hospital inpatients are considered inappropriate [28]. Different approaches have been promoted, and antimicrobial stewardship is currently considered the most promising and has been promoted for all hospitals and health care facilities [29–32]. In 2014, the U.S. Centers for Disease Control and Prevention (CDC) identified seven core elements of antibiotic stewardship and recommend that all hospitals have an antibiotic stewardship program (ASP). Tracking (monitoring process measures), reporting information on antibiotic use and resistance, and education of clinicians and health care providers are three of these core elements [33].

These four antimicrobial agents are an example of antibiotics that have been reserved for the treatment of severe infections, in an attempt to save these valuable drugs from the threat of selection of resistant bacteria. Healing these infections often requires long periods of time of antibiotic therapy and hospitalization. This poses serious concerns, namely regarding plasma accumulation of these drugs, toxicity, and impairment of renal function. Kidneys’ deterioration can be an effect of the disease or a consequence of long-term treatment. Since these antibiotics are mainly renally eliminated and their clearance is an important factor to consider when determining treatment regimens, therapeutic drug monitoring and dose adjustment are imperative to ensure a good clinical outcome of these patients.

In this work, clinical data from a cohort of Portuguese inpatients with severe infections were collected and analyzed, and the influence of therapeutic regimens, biological sex, total body weight, and renal function on the pharmacokinetic (PK) profile was studied for four antibiotics: aminoglycosides amikacin, gentamicin, and tobramycin, and glycopeptide vancomycin. PK studies including physiologically based pharmacokinetic (PBPK) modeling and simulations were performed using GastroPlus™, based on our experience and previous works that have highlighted the value of in silico tools [34–36].

2. Materials and Methods

2.1. Study Population

Demographic data (biological sex, age, weight, and height) and clinical information were collected from 82 inpatients hospitalized in Centro Hospitalar Universitário do Porto (CHUP, Portugal) with severe systemic infections of different etiologies. These patients received intravenous (IV) treatment with one of four antibiotics: aminoglycoside amikacin, gentamicin, or tobramycin, or glycopeptide vancomycin. Drugs were administered via 30-min infusions in the case of aminoglycosides and 1-h infusions for vancomycin. Throughout the hospitalization and treatment period, trough and peak antibiotic concentrations as well as serum creatinine levels were determined to adjust posology and evaluate renal function (estimating creatinine clearance using the Cockcroft–Gault formula [37]). Recommended and followed treatment regimens were also recorded. The gathered information is presented in Supplementary Table S1 and summarized in Table 1.
Table 1. Summary of collected clinical data, with the indication of the average value, lower and upper limits for each parameter. Normal range values (CHUP reference) are also presented.

| Parameter                  | Amikacin | Gentamicin | Tobramycin | Vancomycin |
|----------------------------|----------|------------|------------|------------|
| \(n\) (\(n_{sex}\))       | 8 (F: 1; M: 7) | 22 (F: 8; M: 14) | 5 (F: 4; M: 1) | 47 (F: 21; M: 26) |
| Age (years)                | 14–87 (avg 57) | 7–88 (avg 58) | 13–19 (avg 15) | 19–93 (avg 63) |
| Weight (kg)                | 50.0–92.5 (avg 66.0) | 15.5–85.0 (avg 66.0) | 25.8–44.5 (avg 33.0) | 29.0–140. (avg 69.0) |
| Height (cm)                | 163–180 (avg 169) | 108–185 (avg 165) | 130–158 (avg 146) | 147–185 (avg 163) |
| \(C_{min}\) (mg/L)        | 0.30–16.40 (avg 3.70) | 0.20–4.80 (avg 1.05) | 0.06–0.23 (avg 0.17) | 4.50–45.60 (avg 16.34) |
| \(C_{max}\) (mg/L)        | 19.70–87.80 (avg 38.97) | 2.90–19.50 (avg 9.22) | 16.32–36.12 (avg 27.05) | 11.20–60.10 (avg 25.99) |
| \([\text{Cr}]\) (mg/dL)   | 0.47–1.58 (avg 0.93) | 0.29–1.89 (avg 0.83) | 0.35–0.64 (avg 0.49) | 0.27–4.78 (avg 1.00) |
| CL (L/h) *                 | 1.40–11.30 (avg 6.07) | 1.67–15.89 (avg 5.94) | 3.87–8.77 (avg 6.01) | 0.59–18.80 (avg 5.79) |

* Estimation using the Cockcroft–Gault equation. Ref: normal range (CHUP). CF: Cystic fibrosis.

2.2. Pharmacokinetic Analysis Software

PBPK modeling and simulation software GastroPlus™ version 9.5 (Simulations Plus Inc., Lancaster, CA, USA) was used for the prediction of PK parameters and generation of simulated human plasma concentration profiles. Some physicochemical properties of the four antibiotics and input parameters used in the simulations are presented in Table 2.

Table 2. Physicochemical properties of antibiotics and input parameters in GastroPlus™.

| Parameter                  | Amikacin | Gentamicin | Tobramycin | Vancomycin |
|----------------------------|----------|------------|------------|------------|
| Molecular weight           | 585.61   | 477.61     | 467.52     | 1449.28    |
| logP                       | –5 1     | –1.79 1; –3.1 2 | –4.8 1; –5.8 2 | 2.48 1; –3.1 2 |
| pKa                        | 8.1 2    | 12.55; 10.18 2 | 12.54; 9.83 2 | 2.99; 9.93 2 |
| Solubility                 | 166.49 g/L, pH = 11.73 1; 50 g/L 2 | 56.54 g/L, pH = 11.51 1; 12.6 g/L 2 | 59.47 g/L, pH = 11.34 1; freely soluble 2 | 0.26 g/L, pH = 8.17 1; 0.225 g/L 2 |
| Diffusion Coefficient      | 0.53 cm²/s × 10⁻⁵ 1 | 0.56 cm²/s × 10⁻⁵ 1 | 0.6 cm²/s × 10⁻⁵ 1 | 0.32 cm²/s × 10⁻⁵ 1 |
| Drug particle density      | 1.2 g/mL | 1.2 g/mL | 1.2 g/mL | 1.2 g/mL |
| Mean particle radius       | 25       | 25         | 25         | 25         |
| \(P_{eff}\)                | 0.0202 cm/s × 10⁻⁴ 1 | 0.0891 cm/s × 10⁻⁴ 1 | 0.0368 cm/s × 10⁻⁴ 1 | 0.0747 cm/s × 10⁻⁴ 1 |
| \(F_{up}\)                 | 98.75% 1; >90% 2 | 85.4% 1; >70% 2 | 100% 1; >70% 2 | 21.36% 1; ~50% 2 |
| Blood/plasma ratio         | 1.23 1   | 1.11 1     | 1.31 1     | 0.68 1     |
| \(T_{1/2}\)                | 2–3 h    | 2–3 h      | 2–3 h      | ~6 h (4–11 h) |
| \(V_c\)                   | 0.24 1; ~0.34 L/kg 2 | 0.38 1; 0.2–0.3 L/kg 2 | 0.3 1; 0.2–0.3 L/kg 2 | 0.4–1 L/kg 2 |
| Clearance                  | 6.00 L/h | 3.42 L/h   | 8.48 L/h   | 4.03 L/h   |
| Typical dosing for         | 7.5 mg/kg q12h | 1 mg/kg q8h | 1 mg/kg q8h | 1000 mg q12h |
| susceptible infections     | 15 mg/kg q24h | Variable: 400–800 mg | 1 g q12h 2 | 400 mg q24h |
| Common dosing in CHUP      | q24h or q48h | 120 mg q8h | 70 mg q8h | 1 g q12h 2 |

1 predicted by GastroPlus™; 2 from DrugBank and references [38–44].

GastroPlus™, a powerful mechanistically based simulation and modeling software, has been specifically developed for pharmaceutical research. Physiological parameters of several species, including human, are preinstalled, allowing for the amount of drug that is released, dissolved, and absorbed to be modeled for nine compartments, corresponding to different segments of the digestive tract, based on a set of differential equations. The
Advanced Compartmental Absorption and Transit (ACAT) and Physiologically Based Pharmacokinetic (PBPK) models support model-based drug development throughout multiple stages of drug discovery, translational research, and clinical development, making it a powerful tool. As such, this software has been used in numerous research studies, but also by distinguished pharmaceutical companies and by the U.S. Food and Drug Administration, the U.S. Centers for Disease Control and Prevention, the U.S. National Institutes of Health, the U.S. National Cancer Institute, and the China Food and Drug Administration [45,46]. A PBPK analysis uses models and simulations that combine physiology, population, and drug characteristics to mechanistically describe the PK behavior of a drug. Throughout a drug’s life cycle, PBPK model predictions can be used to support decisions on whether, when, and how to conduct certain clinical pharmacology studies and to support dosing recommendations in product labeling. The predictive performance of PBPK models in specific clinical settings with heterogeneous and chronically ill patients characterized by numerous unknown individual and clinical factors can be developed [47–51].

2.3. PBPK Modeling and Simulation

Every simulation was performed to study the PK for 72 h after IV administrations of each antibiotic, over 30-min infusions for aminoglycosides amikacin, gentamicin and tobramycin, and 1-h infusions for vancomycin.

For each antibiotic, a customized PBPK model was built to represent the average of that subpopulation (receiving treatment with a particular antibiotic). The input parameters were age, total body weight, and renal clearance (Table 1). Different therapeutic regimens (doses and dosing intervals) were studied for each antibiotic, based on the most common schemes administered to the patients in CHUP. Then, the most recurrent therapeutic regimen was chosen for each antibiotic and the influence of biological sex, body weight and renal function was assessed. Customized PBPK models were set up for male and female individuals with the average characteristics of the subpopulation. The effect of body weight and renal function was studied, defining these parameters as the lower and upper limit of the observed range (Table 1), creating 4 additional tailored PBPK models to represent these different conditions: lowest and highest body weight, and lowest and highest renal function, estimated by creatinine clearance.

The available data only included measured concentrations from 2 time points: right before a dose and 1 h (aminoglycosides) or 3 h (vancomycin) after the beginning of an infusion. Since in GastroPlus™ the observed data can only be used as input referring to a single administration, this prevented a further refined parameterization and validation of the developed models. Nevertheless, the predicted pharmacokinetic parameters were reasonably consistent with the observed values after administration of all analyzed doses for these 4 antibiotics.

3. Results

3.1. Influence of Dose Regimens and Biological Sex

Different therapeutic regimens (doses and dosing intervals) were studied for each antibiotic, based on the most common schemes administered to the patients in the study population. The influence of biological sex was also assessed. The simulation-calculated PK parameters are presented in Table 3 and the plasma concentration–time profiles showing the influence of these two factors are presented for each antibiotic in Figures 1–4. As expected for IV infusions, the predicted fraction absorbed (Fa) and bioavailability (F) of all antibiotics were >99%, and a peak in antibiotic concentration was always predicted to be reached at the end of infusions. GastroPlus™ also calculated a direct proportionality of dose with $C_{\text{max}}$ and AUC: doubling the dose increased these PK parameters by 2-fold. Additionally, with shorter time intervals between doses, antibiotic accumulation in plasma was more evident. Regarding biological sex, slight differences were observed between the profiles simulated for male and female subjects; a higher $C_{\text{max}}$, but lower concentrations
until following administration is predicted for male individuals, except for vancomycin, where only differences in $C_{\text{max}}$ were noted.

Table 3. Influence of therapeutic regimens and biological sex on the pharmacokinetic parameters of the four studied antibiotics.

| Drug & Posology | Fa (%) | FDp (%) | F (%) | $C_{\text{max}}$ (mg/L) | $T_{\text{max}}$ (h) | $\text{AUC}_{0-t}$ (µg h/mL) | $\text{AUC}_{0-inf}$ (µg h/mL) | $C_{\text{max}}$ liver (mg/L) |
|----------------|--------|---------|-------|----------------|-----------------|-----------------|-----------------|------------------|
| **Amikacin**   |        |         |       |                 |                 |                 |                 |                  |
| 400 mg q24h    | 99.980 | 99.964  | 99.964| 5.981           | 48.5            | 197.570         | 94.836          | 64.761           |
| 800 mg q24h    | 99.980 | 99.964  | 99.964| 11.962          | 48.5            | 395.150         | 189.670         | 129.520          |
| 800 mg q24h female | 99.978 | 99.960  | 99.960| 11.790          | 48.5            | 395.060         | 209.520         | 128.610          |
| **Gentamicin** |        |         |       |                 |                 |                 |                 |                  |
| 70 mg q12h     | 99.859 | 99.834  | 99.834| 2.981           | 60.5            | 88.971          | 51.345          | 31.524           |
| 120 mg q8h     | 99.653 | 99.838  | 99.838| 3.048           | 64.5            | 163.850         | 81.287          | 31.975           |
| 200 mg q24h    | 99.845 | 99.822  | 99.822| 3.304           | 48.5            | 100.650         | 51.345          | 31.524           |
| 250 mg q24h    | 99.829 | 99.806  | 99.806| 3.246           | 48.5            | 100.630         | 51.345          | 31.524           |
| **Tobramycin** |        |         |       |                 |                 |                 |                 |                  |
| 250 mg q24h    | 99.971 | 99.971  | 99.971| 5.702           | 48.5            | 124.780         | 78.230          | 62.346           |
| 500 mg q24h    | 99.971 | 99.971  | 99.971| 11.403          | 48.5            | 249.570         | 156.460         | 129.520          |
| 420 mg q24h    | 99.969 | 99.969  | 99.969| 9.579           | 48.5            | 209.640         | 131.430         | 104.740          |
| 420 mg q24h female | 99.969 | 99.969  | 99.969| 9.460           | 48.5            | 209.640         | 131.430         | 104.740          |
| **Vancomycin** |        |         |       |                 |                 |                 |                 |                  |
| 500 mg q12h    | 99.929 | 99.921  | 99.921| 16.532          | 61.0            | 517.990         | 452.870         | 30.871           |
| 1000 mg q24h   | 99.926 | 99.921  | 99.921| 25.547          | 49.0            | 518.000         | 477.990         | 50.086           |
| 1000 mg q12h   | 99.929 | 99.921  | 99.921| 31.263          | 61.0            | 1036.000        | 905.740         | 61.742           |
| 1000 mg q12h female | 99.930 | 99.921  | 99.921| 29.202          | 61.0            | 1036.000        | 905.740         | 61.742           |

1 fraction absorbed as a percent of the dose (crossing the lumen and entering enterocytes); 2 percent of the dose that has reached the portal vein; 3 bioavailability; 4 maximum plasma concentration reached in the central compartment, in mg/L; 5 time to reach maximum plasma concentration, in hours; 6 area under the plasma concentration–time curve, in µg h/mL, extrapolated to infinity; 7 area under the plasma concentration–time curve, in µg h/mL, for the time of the simulation; 8 maximum concentration reached in the liver, in mg/L.

Figure 1. Amikacin plasma concentration–time profile showing the influence of therapeutic regimens and biological sex (considering the average of the study population: 57 years old, 66.0 kg, 169 cm, CL = 6.07 L/h).

3.2. Influence of Total Body Weight

Concerning body composition, the influence of total body weight was assessed, and the resulting PK parameters are presented in Table 4. As expected, simulations for patients with a lower weight result in a higher $C_{\text{max}}$ and higher drug concentrations maintained throughout time. The plasma concentration–time profiles showing the influence of this parameter are shown for each antibiotic in Figures 5–8.
Figure 2. Gentamicin plasma concentration–time profile showing the influence of therapeutic regimens and biological sex (considering the average of the study population: 58 years old, 66.0 kg, 165 cm, CL = 5.94 L/h).

Figure 3. Tobramycin plasma concentration–time profile showing the influence of therapeutic regimens and biological sex (considering the average of the study population: 15 years old, 33.0 kg, 146 cm, CL = 6.01 L/h).

Table 4. Influence of total body weight on the pharmacokinetic parameters of the four studied antibiotics.

| Drug & Posology       | Fa (%) 1 | Fdp (%) 2 | F (%) 3 | C <sub>max</sub> (mg/L) 4 | T <sub>max</sub> (h) 5 | AUC<sub>0-<inf>inf</inf></sub> (µg h/mL) 6 | AUC<sub>0-t</sub> (µg h/mL) 7 | C <sub>max liver</sub> (mg/L) 8 |
|-----------------------|----------|-----------|---------|---------------------------|------------------------|-------------------------------|-------------------------------|-----------------------------|
| **Amikacin**          |          |           |         |                           |                        |                               |                               |                             |
| 800 mg q24h BW avg (66.0 kg) | 99.980   | 99.964    | 99.964  | 11.962                    | 48.5                   | 395.150                       | 189.670                       | 129.520                     |
| 800 mg q24h BW min (50.0 kg) | 99.981   | 99.965    | 99.965  | 14.813                    | 48.5                   | 395.250                       | 223.520                       | 161.780                     |
| 800 mg q24h BW max (92.5 kg) | 99.982   | 99.966    | 99.966  | 9.161                     | 48.5                   | 394.940                       | 151.390                       | 97.834                      |
| **Gentamicin**        |          |           |         |                           |                        |                               |                               |                             |
| 200 mg q24h BW avg (66.0 kg) | 99.845   | 99.822    | 99.822  | 3.304                     | 48.5                   | 100.650                       | 51.345                       | 31.876                      |
| 200 mg q24h BW min (15.5 kg) | 99.910   | 99.905    | 99.905  | 9.555                     | 48.5                   | 100.890                       | 90.418                       | 97.446                      |
| 200 mg q24h BW max (85.0 kg) | 99.680   | 99.656    | 99.656  | 9.546                     | 48.5                   | 100.630                       | 90.200                       | 97.126                      |
Table 4. Cont.

| Drug & Posology | Fa (%) | FDp (%) | F (%) | Cmax (mg/L) | Tmax (h) | AUC0-inf (µg h/mL) | AUC0-t (µg h/mL) | Cmax liver (mg/L) |
|-----------------|--------|---------|-------|-------------|---------|--------------------|-----------------|------------------|
| Tobramycin      |        |         |       |             |         |                    |                 |                  |
| 420 mg q24h BW avg (33.0 kg) | 99.971 | 99.971 | 99.971 | 9.579 | 48.5 | 209.640 | 131.430 | 104.740 |
| 420 mg q24h BW min (25.8 kg) | 99.973 | 99.973 | 99.973 | 11.479 | 48.5 | 209.660 | 1036.300 | 82.333 |
| 420 mg q24h BW max (44.5 kg) | 99.970 | 99.970 | 99.970 | 7.646 | 48.5 | 209.600 | 1036.000 | 95.749 |

| Vancomycin      |        |         |       |             |         |                    |                 |                  |
| 1000 mg q12h BW avg (69.0 kg) | 99.929 | 99.921 | 99.921 | 31.263 | 61.0 | 1036.000 | 905.740 | 61.742 |
| 1000 mg q12h BW min (29.0 kg) | 99.956 | 99.954 | 99.954 | 48.459 | 61.0 | 1036.000 | 1005.000 | 95.749 |
| 1000 mg q12h BW max (140.0 kg) | 99.936 | 99.926 | 99.926 | 22.535 | 61.0 | 1035.800 | 736.330 | 44.587 |

1 fraction absorbed as a percent of the dose (crossing the lumen and entering enterocytes); 2 percent of the dose that has reached the portal vein; 3 bioavailability; 4 maximum plasma concentration reached in the central compartment, in mg/L; 5 time to reach maximum plasma concentration, in hours; 6 area under the plasma concentration–time curve, in µg h/mL; 7 area under the plasma concentration–time curve, extrapolated to infinity; 8 maximum concentration reached in the liver, in mg/L.

Figure 4. Vancomycin plasma concentration–time profile showing the influence of therapeutic regimens and biological sex (considering the average of the study population: 63 years old, 69.0 kg, 163 cm, CL = 5.79 L/h).

Figure 5. Amikacin plasma concentration–time profile showing the influence of body weight (for an 800 mg q24h dose, considering a male individual with the average characteristics of the study population: 57 years old, 169 cm, CL = 6.07 L/h).
extrapolated to infinity; area under the plasma concentration–time curve, in µg∙h/mL, for the time of the simulation; maximum concentration reached in the liver, in mg/L.

Figure 5. Amikacin plasma concentration–time profile showing the influence of body weight (for an 800 mg q24h dose, considering a male individual with the average characteristics of the study population: 57 years old, 169 cm, CL = 6.07 L/h).

Figure 6. Gentamicin plasma concentration–time profile showing the influence of body weight (for a 200 mg q24h dose, considering a male individual with the average characteristics of the study population: 58 years old, 165 cm, CL = 5.94 L/h).

Figure 7. Tobramycin plasma concentration–time profile showing the influence of body weight (for a 420 mg q24h dose, considering a male individual with the average characteristics of the study population: 15 years old, 146 cm, CL = 6.01 L/h).

Figure 8. Vancomycin plasma concentration–time profile showing the influence of body weight (for a 1000 mg q12h dose, considering a male individual with the average characteristics of the study population: 63 years old, 163 cm, CL = 5.79 L/h).

3.3. Influence of Renal Function

Finally, the influence of renal function was evaluated. This is a particularly relevant consideration, since during treatment (especially for long periods of time), kidneys can be affected as a side effect of medication, and renal function is often impaired. The PBPK simulations confirmed this, and CL\textsubscript{Cr} was the most significantly impacting factor on antibiotics plasma concentrations. PK parameters are presented in Table 5 and plasma concentration–time profiles are illustrated for each antibiotic in Figures 9–12.
3.3. Influence of Renal Function

Finally, the influence of renal function was evaluated. This is a particularly relevant consideration, since during treatment (especially for long periods of time), kidneys can be affected as a side effect of medication, and renal function is often impaired. The PBPK modeling of the four studied antibiotics demonstrated the importance of renal function on the pharmacokinetic parameters. The following table summarizes the influence of creatinine clearance (CL\textsubscript{Cr}) on the pharmacokinetic parameters of each antibiotic:

| Drug & Posology | Fa (%) \textsuperscript{1} | FDP (%) \textsuperscript{2} | F (%) \textsuperscript{3} | C\textsubscript{max} (mg/L) \textsuperscript{4} | T\textsubscript{max} (h) \textsuperscript{5} | AUC\textsubscript{0-inf} (µg·h/mL) \textsuperscript{6} | AUC\textsubscript{0-t} (µg·h/mL) \textsuperscript{7} | C\textsubscript{max liver} (mg/L) \textsuperscript{8} |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Amikacin**    |                 |                 |                 |                 |                 |                 |                 |                 |
| 800 mg q24h CL avg (6.068 L/h) | 99.980 | 99.964 | 99.964 | 11.962 | 48.5 | 395.150 | 189.670 | 129.520 |
| 800 mg q24h CL min (1.401 L/h) | 99.974 | 99.950 | 99.950 | 13.293 | 48.5 | 1705.900 | 258.260 | 147.360 |
| 800 mg q24h CL max (11.298 L/h) | 99.985 | 99.973 | 99.973 | 11.015 | 48.5 | 212.320 | 142.930 | 117.190 |
| **Gentamicin**  |                 |                 |                 |                 |                 |                 |                 |                 |
| 200 mg q24h CL avg (5.941 L/h) | 99.845 | 99.822 | 99.822 | 3.304 | 48.5 | 100.650 | 51.345 | 31.876 |
| 200 mg q24h CL min (1.667 L/h) | 99.789 | 99.751 | 99.751 | 3.667 | 48.5 | 355.600 | 69.999 | 36.212 |
| 200 mg q24h CL max (15.887 L/h) | 99.908 | 99.899 | 99.899 | 2.860 | 48.5 | 37.744 | 30.152 | 26.809 |
| **Tobramycin**  |                 |                 |                 |                 |                 |                 |                 |                 |
| 420 mg q24h CL avg (6.007 L/h) | 99.971 | 99.971 | 99.971 | 9.579 | 48.5 | 209.640 | 131.430 | 104.740 |
| 420 mg q24h CL min (3.868 L/h) | 99.965 | 99.965 | 99.965 | 10.149 | 48.5 | 325.460 | 158.850 | 111.740 |
| 420 mg q24h CL max (8.771 L/h) | 99.977 | 99.977 | 99.977 | 9.032 | 48.5 | 143.600 | 106.330 | 98.209 |
| **Vancomycin**  |                 |                 |                 |                 |                 |                 |                 |                 |
| 1000 mg q12h CL avg (5.787 L/h) | 99.929 | 99.921 | 99.921 | 31.263 | 61.0 | 1036.000 | 905.740 | 61.742 |
| 1000 mg q12h CL min (0.590 L/h) | 99.789 | 99.743 | 99.743 | 73.192 | 61.0 | 1090.000 | 2659.400 | 146.400 |
| 1000 mg q12h CL max (18.796 L/h) | 99.976 | 99.974 | 99.974 | 19.356 | 61.0 | 319.140 | 313.790 | 38.136 |

\textsuperscript{1} fraction absorbed as a percent of the dose (crossing the lumen and entering enterocytes); \textsuperscript{2} percent of the dose that has reached the portal vein; \textsuperscript{3} bioavailability; \textsuperscript{4} maximum plasma concentration reached in the central compartment, in mg/L; \textsuperscript{5} time to reach maximum plasma concentration, in hours; \textsuperscript{6} area under the plasma concentration–time curve, in µg·h/mL, extrapolated to infinity; \textsuperscript{7} area under the plasma concentration–time curve, in µg·h/mL, for the time of the simulation; \textsuperscript{8} maximum concentration reached in the liver, in mg/L.

When considering the lowest CL\textsubscript{Cr}, antibiotic concentrations are much higher in comparison to individuals with normal functioning kidneys. This is exceptionally important in the case of vancomycin, where the differences between the lower and upper limits of observed CL\textsubscript{Cr} were exceedingly significant.
### Table 5.

| Drug     | Dose       | CL max (L/h) | AUC0-t (µg ∙ h/mL) |
|----------|------------|--------------|--------------------|
| Amikacin | 800 mg q24h| 11.298       | 212.320            |
|          | 200 mg q24h| 15.887       | 37.744             |
|          | 1000 mg q12h| 18.796      | 10090.000          |
|          | 420 mg q24h| 8.771        | 143.600            |
|          | 420 mg q24h| 3.868        | 325.460            |
| Gentamicin | 800 mg q24h| 11.30       | 212.320            |
|          | 200 mg q24h| 15.89       | 37.744             |
|          | 1000 mg q12h| 18.796      | 10090.000          |
|          | 420 mg q24h| 8.771        | 143.600            |
|          | 420 mg q24h| 3.868        | 325.460            |

#### Figure 9. Amikacin plasma concentration–time profile showing the influence of renal function (for an 800 mg q24h dose, considering a male individual with the average characteristics of the study population: 57 years old, 66.0 kg, 169 cm).

#### Figure 10. Gentamicin plasma concentration–time profile showing the influence of renal function (for a 200 mg q24h dose, considering a male individual with the average characteristics of the study population: 58 years old, 66.0 kg, 165 cm).

#### 3.4. Effect of Renal Function on the Accumulation of Drugs in Plasma over Time

Since the influence of renal function on the PK profile of the antibiotics was so significant, the observed differences were further analyzed.

The differences in the predicted antibiotics concentrations at 72 h between the simulation for the lowest and average CL, and lowest and highest CL were calculated (Figure 13). For the simulations customized to represent the patients with the lowest CL, the differences between the \( C_{\text{peak}} \) of the last and \( C_{\text{peak}} \) of the first administrations were also determined (Figure 14). As aforementioned, renal function has a major impact on the plasma concentration profile of antibiotic vancomycin. As such, it is particularly important to closely observe patients receiving this antibiotic, monitoring their drug’s plasma concentration and changes in their renal function. Vancomycin can easily accumulate and rapidly reach toxic levels in plasma, which can lead to severe adverse effects and cause permanent damage to the kidneys.
Figure 11. Tobramycin plasma concentration–time profile showing the influence of renal function (for a 420 mg q24h dose, considering a male individual with the average characteristics of the study population: 15 years old, 33.0 kg, 146 cm).

Figure 12. Vancomycin plasma concentration–time profile showing the influence of renal function (for a 1000 mg q12h dose, considering a male individual with the average characteristics of the study population: 63 years old, 69.0 kg, 163 cm).

Figure 13. Influence of renal function on the accumulation of the antibiotics in plasma throughout treatment: difference in the plasma concentration at 72 h.
especially vancomycin, but that there are certainly other factors affecting PK and more optimizations to be made to these PBPK models, since the values obtained in the simulations may come even closer to those observed clinically. In particular, it is known that hospitalized and critically ill patients have altered PK and the fact that in this project it was not possible, due to software limitation, to insert the observed concentrations into the models, refining, optimizing, and then validating them, also contributed to the slight differences between the simulated and clinical results.

The results presented here deepen the knowledge on the impact and influence of these parameters on the biodistribution of these antibiotics. This is crucial not only to ensure a successful clinical outcome, but also to prevent serious side effects, and, as such, can assist clinicians in the process of adjusting therapeutic regimens. In this context, the helpfulness of in silico tools, such as PBPK modeling and software such as GastroPlus™, was also verified.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/life11111130/s1, Table S1: Demographic information and clinical data of the study population.

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