



## Review

# Clinical applications of population pharmacokinetic models of antibiotics: Challenges and perspectives



Femke de Velde<sup>a,\*</sup>, Johan W. Mouton<sup>a</sup>, Brenda C.M. de Winter<sup>a,b</sup>, Teun van Gelder<sup>b</sup>, Birgit C.P. Koch<sup>b</sup>

<sup>a</sup> Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands

<sup>b</sup> Department of Hospital Pharmacy, Erasmus University Medical Center, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands

## ARTICLE INFO

### Chemical compounds studied in this article:

Vancomycin (CID: 14969)  
 Amoxicillin (CID: 33613)  
 Gentamicin (CID: 3467)  
 Ciprofloxacin (CID: 2764)  
 Amikacin (CID: 37768)  
 Levofloxacin (CID: 149096)  
 Ceftazidime (CID: 5481173)  
 Cefotaxime (CID: 2632)  
 Tobramycin (CID: 36294)

### Keywords:

Anti-bacterial agents  
 Population pharmacokinetics  
 PK/PD  
 Therapeutic drug monitoring  
 Individualized dosing

## ABSTRACT

Because of increasing antimicrobial resistance and the shortage of new antibiotics, there is a growing need to optimize the use of old and new antibiotics. Modelling of the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of antibiotics can support the optimization of dosing regimens. Antimicrobial efficacy is determined by susceptibility of the drug to the microorganism and exposure to the drug, which relies on the PK and the dose. Population PK models describe relationships between patients characteristics and drug exposure. This article highlights three clinical applications of these models applied to antibiotics: 1) dosing evaluation of old antibiotics, 2) setting clinical breakpoints and 3) dosing individualization using therapeutic drug monitoring (TDM). For each clinical application, challenges regarding interpretation are discussed. An important challenge is to improve the understanding of the interpretation of modelling results for good implementation of the dosing recommendations, clinical breakpoints and TDM advices. Therefore, also background information on PK/PD principles and approaches to analyse PK/PD data are provided.

## 1. Introduction

Increasing antimicrobial resistance and the shortage of new antibiotics have emphasized the importance of optimizing dosing regimens of old and new antibiotics in order to improve clinical outcomes of infections [1]. Modelling of the pharmacokinetic and pharmacodynamic (PK/PD) characteristics of antibiotics can support the optimization of dosing regimens. PK/PD of antibiotics describe the relationship between efficacy, the *in vitro* susceptibility of a drug to the microorganism (usually expressed as MIC, minimal inhibitory concentration) and the *in vivo* exposure to the drug, which relies on the PK and the dose (Fig. 1) [1]. From this relationship follows that if the MIC is known, the microbiological and clinical outcome of treatment is determined by the individual PK profile and dose. To predict that exposure, population PK models can and are being used. The quality of the model used will determine the value of the estimated exposure.

During new drug development, population PK models of antibiotics are recommended to use for optimizing dosing regimens [2]. Population PK models are also used to improve dosing regimens of old antibiotics in current use and to individualize treatment in the clinical setting. Many currently used antibiotics were developed and approved decades ago when PK/PD principles were largely unknown and sophisticated population PK modelling techniques did not exist [3]. Nowadays, some of these old antibiotics are studied again and an increasing number of population PK models are published with new dosing recommendations for specific populations.

Sufficient understanding of the interpretation of modelling results is essential for good implementation of these dosing recommendations. Therefore, this article provides background information on the PK/PD principles of antibiotics (Section 2) and the different approaches of analyzing PK/PD data (Section 3) with the objective to understand the published population PK models and their clinical applications. Section

**Abbreviations:** ECOFF, EUCAST epidemiological cut-off value; EUCAST, European committee on antimicrobial susceptibility testing; MIC, minimal inhibitory concentration; MCS, Monte Carlo simulations; PTA, probability of target attainment

\* Corresponding author.

E-mail address: [f.develde@erasmusmc.nl](mailto:f.develde@erasmusmc.nl) (F. de Velde).

<https://doi.org/10.1016/j.phrs.2018.07.005>

Received 24 May 2018; Received in revised form 5 July 2018; Accepted 5 July 2018

Available online 06 July 2018

1043-6618/© 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

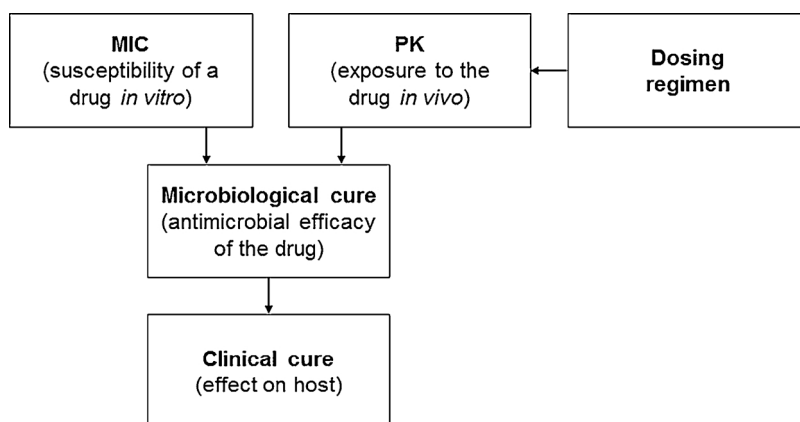


Fig. 1. Relationship between MIC, PK, dose and drug effects.

4 discusses the clinical applications of population PK models of antibiotics (dosing evaluation of old antibiotics, setting clinical MIC breakpoints and therapeutic drug monitoring) including challenges regarding the interpretation of modelling results.

## 2. PK/PD principles of antibiotics

### 2.1. PK/PD indices

PK/PD indices describe exposure-response relationships. A PK/PD index represents the relationship between a PK measure of exposure to the antibacterial agents (such as AUC, area under the concentration-time curve, or  $C_{max}$ , maximal concentration) and a PD measure of bacterial susceptibility to the drug (usually the MIC).

Only the non-protein-bound fraction of an antibiotic is microbologically active and can penetrate into the extravascular space [4]. Therefore, PK/PD indices are based on unbound concentrations.

For each antibiotic, different PK/PD indices (such as AUC/MIC,  $C_{max}/MIC$  and  $T > MIC$ , Fig. 2) are tested in preclinical studies to identify which PK/PD index is most likely to be associated with efficacy. PK/PD indices are different for each antibacterial class [5]. For example, the PK/PD index of beta-lactams is the percentage of the dosing interval that the unbound (free) antibiotic concentration is above the MIC ( $\%fT > MIC$ ) [5] and the PK/PD index of vancomycin is  $fAUC_{0-24}/MIC$  [6].

### 2.2. PK/PD targets

The PK/PD target is the minimal PK/PD index value that ensures a high probability of successful treatment [1]. There is no unique PK/PD target value per antibiotic. PK/PD target values vary between the

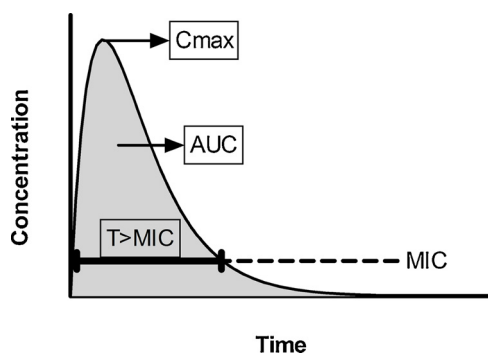


Fig. 2. Concentration-time curve showing the pharmacokinetic parameters  $C_{max}$  (maximal concentration) and AUC (shaded area) and the PK/PD index  $T > MIC$ .

chosen endpoints such as stasis, maximal kill or resistance suppression (for preclinical studies) and microbiological or clinical cure (for clinical studies) [7,8].

To attain a specific PK/PD target, the exposure of the microorganism to the antibacterial agent needs to be adequate. This exposure is dependent on the dose and PK properties of the drug.

#### 2.2.1. Challenge: PK/PD target values

The optimal PK/PD target value is still not clearly defined for all antibiotics [9], in part because this depends on its clinical indication or use. For example, for beta-lactam antibiotics, used targets vary between 40–100%  $fT > MIC$  and 50–100%  $fT > 4xMIC$  [7,10,11]. Currently, there is a trend towards the use of more conservative targets for critically ill patients than for the less critically ill. However, it may be possible that this assumption is the consequence of variation in MIC measurements [12]. More research in this area is clearly required. It is also important to realize that preclinical derived PK/PD target values differ from clinical derived values in critically ill patients [7].

#### 2.2.2. Challenge: protein binding

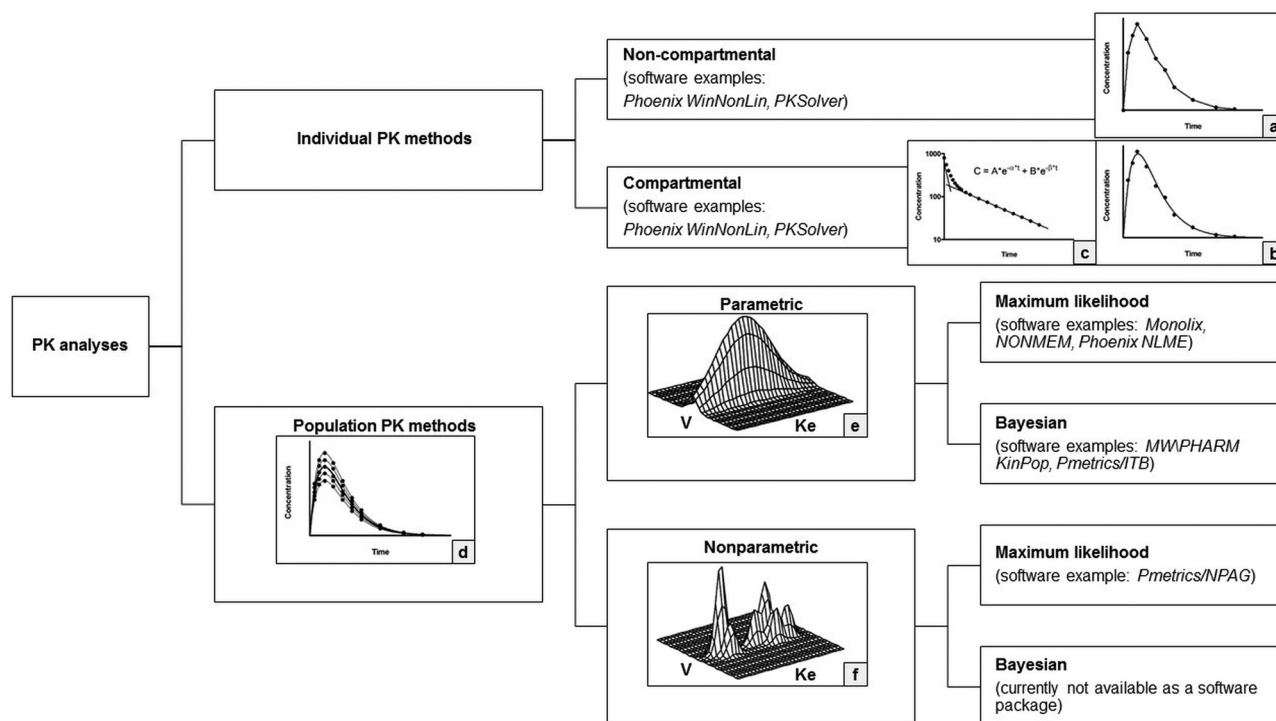
PK/PD indices and targets are (almost) always defined as free (unbound) concentrations whereas many assays measure total (unbound and protein bound) concentrations [4,13]. However, protein binding is often highly variable and hypoalbuminemia occurs frequently in critically ill patients [14,15], which might lead to unreliable outcomes if a free concentration is calculated using a literature value for protein binding. In addition, protein binding can be concentration dependent and even nonlinear [16–18].

#### 2.2.3. Challenge: site of measurement

Most PK/PD targets are based on blood levels. However, other body sites may be important as well, although the interpretation for these body sites still remains uncertain [2]. If there is a good correlation between plasma levels and body site levels this is not a major problem, as this is just a shift in target values. If the correlation is less predictable this may become a major issue [19]. For instance in the very obese patients, tissue concentrations can be much lower than expected [20].

### 2.3. Clinical breakpoints

Information about the PK/PD target, PK characteristics, exposure, variability and dosing regimens is needed to set clinical breakpoints. Clinical breakpoints are MICs that define microorganisms as susceptible, intermediate or resistant to specific antibiotics [21]. Clinical breakpoints determine the antibacterial choice during empirical and culture-driven therapy.



**Fig. 3.** Overview of PK analysis methods. a) Non-compartmental analysis: connection of individual concentrations by linear interpolation; b) and c) Compartmental analysis: fitting of individual concentrations into a compartmental model equation (b: linear y-axis, oral administration, 1 distribution compartment. c: logarithmic y-axis, intravenous administration, 2 distribution compartments); d) Population PK data; e) Parametric and f) Nonparametric analysis of population PK data with 2 subpopulations of slow (low  $K_e$ , elimination constant) and fast (high  $K_e$ ) metabolizers. The parametric method assumes that the data are normally distributed whereas the nonparametric method identifies the 2 subpopulations. e) and f) Reprinted with permission of the *Laboratory of Applied Pharmacokinetics* [36].

### 3. PK analyses and simulations

PK describes the behaviour of drugs and their metabolites in the body in terms of absorption, distribution, metabolism and elimination. Concentration-time courses are related to the dose received and subject characteristics. PK analysis methods can be distinguished between individual (paragraph 3.1) and population approaches (3.2), which can be further classified as parametric, nonparametric, maximum likelihood and Bayesian methods (Fig. 3).

Population PK models can be used to perform simulations (3.3) to evaluate models (internal or external validation) and dosing regimens. For the latter purpose, the probability of target attainment (PTA, 3.3.1) can be calculated.

#### 3.1. Individual PK methods

Individual PK methods analyse concentration-time courses per individual subject. Examples of individual PK methods are the non-compartmental analysis and the standard-two-stage method.

Non-compartmental analysis (NCA) is the simplest individual PK method. NCA applies no model to the data but connects the observed individual concentrations by linear interpolation.

The standard two-stage (STS) method fits the data of each individual separately into a compartmental model equation and then combines individual parameter estimates to generate mean (population) parameters and standard deviations [22].

Individual PK methods are relatively simple techniques and useful to explore datasets and calculate PK measures as AUC and  $C_{max}$ . However, they don't provide detailed information (e.g. covariates) on variation of PK parameters in a population. Another disadvantage is that these methods require intensive sampling. Examples of individual PK software packages are Phoenix WinNonlin and PKSolver [23]. In addition to NCA and/or STS methods, some of the individual PK packages also offer population PK methods.

#### 3.2. Population PK methods

Population PK methods analyse concentration-time courses of a population as a whole. During the modelling process, several models with different numbers of compartments, types of elimination and variability are evaluated. The final model provides mean population PK parameters (e.g. volume of distribution, clearance) and describes variability between subjects (inter-individual or between-subject variability, BSV) and variability between the doses of an individual subject (intra-individual or between-occasion variability, BOV). The observed variability is explained by covariates (subject characteristics as body weight, renal function or age). Residual variability (e.g. assay variance or sampling uncertainties) is also taken in account [22,24].

Thorough model evaluation and validation is important to deliver a robust and reliable model. Examples of model evaluation/validation methods and techniques are objective functions based on likelihood (e.g. AIC, Akaike Information Criterion), graphical plots, bootstrapping to estimate parameter precision, simulation-based diagnostics (e.g. VPC, Visual Predictive Check, or NPDE, Normalized Prediction Distribution Error) and external validation, when the developed model is applied to a new dataset [24,25].

Traditionally, population PK parameters were estimated by the standard two-stage “individual” approach, which cannot describe and explain the types of variability. More sophisticated population PK methods involve the development of nonlinear mixed-effect models. These models are called “nonlinear” because PK equations are nonlinear. “Mixed-effect” implies the description of fixed effects (which are the same for each individual) and random (individual-specific) effects.

Population PK modelling methods can be statistically classified as either parametric or nonparametric. The parametric and nonparametric classifications can both be divided into maximum likelihood or Bayesian approaches [26,27]. The different modelling approaches will be briefly described here.

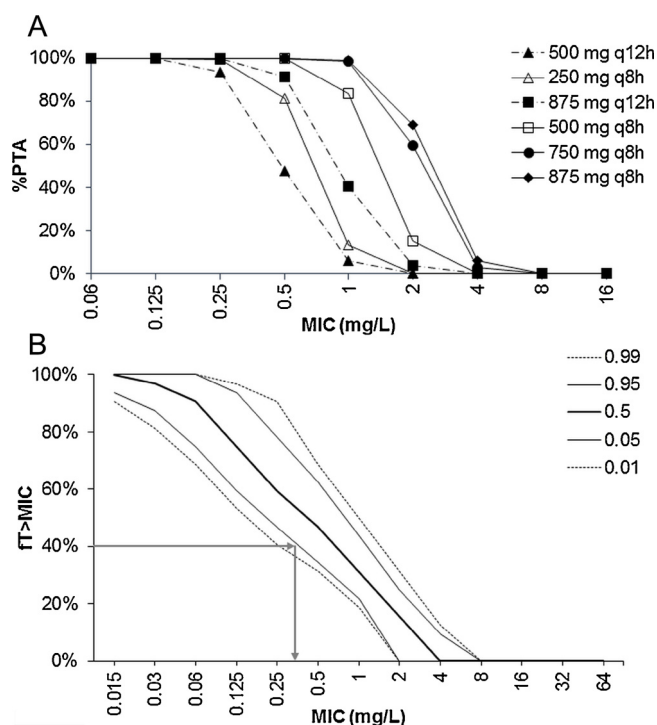


Fig. 4. (a) PTA for various amoxicillin dosing regimens to reach the target 40%  $fT > MIC$  for a range of MICs. Modified from [35]. (b)  $\%fT > MIC$  displayed as a function of the MIC for amoxicillin 250 mg q8h. Modified from [35].

### 3.2.1. Parametric maximum likelihood methods

Parametric maximum likelihood methods assume that the population parameter distribution is known with unknown population parameters [27]. These methods estimate the set of parameters that maximize the joint likelihood of observations. Most of the current software packages for population PK modelling are parametric maximum likelihood methods (e.g. Monolix, NONMEM and Phoenix NLME). Each package offers one or more mathematic algorithms to facilitate maximum likelihood modelling, such as FOCE, SAEM or QRPEM [28].

### 3.2.2. Nonparametric maximum likelihood methods

In contrast to parametric methods, nonparametric methods make no assumption about the shapes of the underlying parameter distributions, which is theoretically an advantage to detect subpopulations. Nonparametric methods use an exact likelihood function while parametric methods use an approximation. A drawback of nonparametric methods is that confidence intervals about parameter estimates are not easily determined [26,27]. An example of a nonparametric maximum likelihood method is the NPAG algorithm in the software package Pmetrics (former MM-USCPACK / USC\*PACK, previously based on the NPEM algorithm) [29].

### 3.2.3. Bayesian methods

The parametric iterative two-stage Bayesian (ITB) method uses mean parameter values and their standard deviations (obtained from a STS method or any reasonable initial guess) as Bayesian priors. Subsequently, individual patient data are examined to obtain Bayesian posterior parameter values based on the maximum a posteriori probability (MAP) Bayesian procedure. The mean parameter values can again be calculated and used as Bayesian priors to obtain new Bayesian posterior values. This iterative process is repeated until the difference between population and estimated values reaches a minimum value [30,31]. Examples of software packages including the ITB method are the KinPop module in MWPHARM [31] and the ITB algorithm in Pmetrics, which is mainly used to estimate parameter ranges to be

passed to NPAG [29].

A nonparametric Bayesian approach is currently not available in a software package [26].

### 3.2.4. Challenges: population PK approaches

It is still unknown which population PK approach (e.g. parametric vs nonparametric) is most suitable for specific research questions. More studies comparing both methods are warranted.

A drawback of many modelling studies is that the sample size is usually small and that sample size calculation is lacking [7,32].

## 3.3. Simulations

For clinical applications, simulations using population PK models are generally performed for two purposes: 1) model evaluation and 2) dosing evaluation [22]. For model evaluation, concentration-time data are simulated and compared with a subset of the original dataset (internal validation) or new data (external validation). For dosing evaluation, concentration-time data are simulated for several dosing regimens to study the exposure and probability of target attainment (PTA, see 3.3.1), for example in specific subpopulations such as ICU-patients or patients with renal impairment [22,33], or during the process of setting breakpoints [21].

Stochastic simulating from population PK models with fixed-effect and random-effect parameters is more complex than non-stochastic simulating from simple fixed-effect models. The stochastic Monte Carlo simulation (MCS) can handle random variability and is therefore the most used simulation type for population PK models [33,34].

### 3.3.1. Probability of target attainment (PTA)

MCS based on population PK models can be used to calculate the PTA of specific PK/PD targets for several dosing regimens and a range of MICs [21,33]. Different methods are used to present the PTA results. One option is to plot (Fig. 4a) or tabulate the PTA of a specific PK/PD target as a function of the MIC. Several dosing regimens can be included in such a graph (or table). A disadvantage of this approach is that only one PK/PD target value can be included per graph. Since the optimal PK/PD target values are not defined for all antibiotics and indications (see 2.2.1), it may be useful to display several target values in one graph. The latter is possible in the graph shown in Fig. 4b: the PK/PD target (here:  $\%fT > MIC$ ) is plotted as a function of the MIC for a specific dosing regimen. By including the mean (or median) of the population and the confidence interval (CI) estimations (percentiles) in the graph, the PTA's for several PK/PD target values can be read. The lower boundary of a CI of 95% corresponds to a PTA of 97.5%. For example, in Fig. 4b, the PTA for 40%  $fT > MIC$  is 97.5% for 250 mg q8h and an MIC of 0.25 mg/L. EUCAST (European committee on antimicrobial susceptibility testing) uses such graphs to determine breakpoints [21].

## 4. Clinical applications of population PK models

Population PK models are not only used during new drug development [2], but also have various clinical applications after the drug becomes available to the market. From the perspective of antibiotics, three main clinical applications can be specified: 1) dosing evaluation of old antibiotics, 2) setting clinical breakpoints and 3) therapeutic drug monitoring. The applications will be described in paragraphs 4.1–4.3 including the most important challenges regarding their clinical interpretation (Table 1).

### 4.1. Dosing evaluation of old antibiotics

As described in paragraph 3.3, simulations using population PK models can be performed to evaluate dosing regimens and subsequently predict PTAs for different dosing regimens and MICs. Dosing

**Table 1**

Challenges per clinical application of population PK models. The degree of importance is scored with ++ (highly important), + (important), - (not applicable). The most important challenges are further clarified in the text (the respective paragraph is indicated between brackets).

Challenges	Clinical applications of population PK models		
	1. Dosing evaluation of old antibiotics	2. Setting clinical breakpoints	3. Therapeutic drug monitoring
PK/PD targets	++ (2.2.1, 4.1.2)	++ (2.2.1)	++ (2.2.1)
Protein binding	++ (2.2.2)	++ (2.2.2)	++ (2.2.2)
Site of measurement	++ (2.2.3)	++ (2.2.3)	++ (2.2.3)
Clinical validation	++ (4.1.1)	+	++ (4.3.4)
PTA interpretation	++ (4.1.3)	++	-
Population PK model selection	+	+	++ (4.3.5)
Assay availability	+	+	++ (4.3.6)
MIC accuracy and variation	+	+	++ (4.3.7)

recommendations based on such PTA simulations are increasingly published by several research groups [37–42]. Although these publications are filling knowledge gaps for dosing in specific subgroups, their recommendations should be carefully considered because clinical validation is often lacking (4.4.1) and the choice of the PK/PD target value (4.4.2) and PTA acceptance levels (4.4.3) might be questionable. The latter does not belong to the EUCAST rationale documents for which an exhaustive procedure is published [21].

#### 4.1.1. Challenge: clinical validation

The most important concern is that clinical validation of the new dosing recommendations is often lacking. It is desirable that future clinical validation studies not only focus on target achievement, but also relate the exposure to clinical outcomes. A recent review about the PK/PD of gentamicin and other aminoglycosides [32] found that only 1 study prospectively evaluated model-based dosing recommendations to see what exposure actually was achieved in clinically practice [43].

Another example of a dosing recommendation which was hardly prospectively validated, is ciprofloxacin, which is illustrated in paragraph 4.1.1.1.

**4.1.1.1. Example: ciprofloxacin.** Ciprofloxacin is a frequently prescribed fluoroquinolone. The pharmacodynamic target of  $AUC_{0-24}/MIC > 125$  (or  $fAUC_{0-24}/MIC > 100$ ) for *Pseudomonas aeruginosa* is well established in *in vitro*, animal and clinical studies [44–46]. According to the manufacturer, for most indications, the recommended dosing regimen of intravenous ciprofloxacin is 400 mg twice or three times daily in patients with normal renal function [47,48], which implies that the dosing frequency can be chosen by the prescribing physician. However, an increasing number of simulation studies using population PK models show that a dosing regimen of 1200 mg/day is necessary to attain the pharmacodynamic target of  $AUC_{0-24}/MIC > 125$  (or 100 for unbound drug) for Gram-negative pathogens with an  $MIC \geq 0.5$  mg/L [46,49–52].

A major drawback of these studies is that the dosing recommendations of 400 mg q8h for  $MICs \geq 0.5$  mg/L were based on simulations and not prospectively validated. The majority of the study population received a daily dose of maximally 800 mg/day.

Despite the fact that these studies resulted in the same conclusion, the study designs were remarkable different. Some study populations were only ICU patients [49,51] while other study populations also included general ward patients [46,50,52]. Some studies reduced the dose in patients with impaired renal function, each using a different dosing algorithm [46,50,52], while in other studies dose reduction was not applied [49,51]. Translation of these recommendations to clinical

practice is therefore difficult. Even the EMA and FDA provide different dosing recommendations for ciprofloxacin in patients with impaired renal function [47,53].

#### 4.1.2. Challenge: PK/PD targets

As discussed in 2.2.1, the PK/PD targets for some antibiotics and populations are still unclear [3]. Some authors use two or more targets and give different dosing recommendations depending on the target [37]. The previously mentioned review about gentamicin [32] showed that the chosen targets in 7 simulation studies in adults varied between  $C_{max} \geq 8$  mg/L,  $C_{max} > 10$  mg/L,  $C_{max} = 22$  mg/L,  $C_{max}/MIC > 8$ ,  $C_{max}/MIC \geq 10$ ,  $AUC_{24}$  70–120 mg\*h/L and  $AUC_{48} > 140$  mg\*h/L.

#### 4.1.3. Challenge: PTA interpretation

Another problem is that PTA interpretation is not standardized. Used PTA acceptance levels vary between 90–100% and are sometimes not even mentioned. However, it is important to realize that a PTA of 90% means that 10% of the patients do not attain the target for a specific MIC, which implicates that the probability for successful treatment is diminished. For new antimicrobials, the EMA indicates a PTA of 90% for dose selection [2].

The chosen MICs for the dosing recommendations should always be weighed against the internationally published MIC clinical breakpoints. EUCAST uses the MIC values based on PTA's of 97.5% and 99% for setting breakpoints [21].

#### 4.2. Setting clinical breakpoints

The EUCAST provides species-related and PK/PD (non-species related) clinical breakpoints. The EUCAST procedure for setting PK/PD breakpoints includes MCS using population PK models to estimate exposure of an antimicrobial agent in the target patient population for commonly used dosing regimens [21]. Following the simulations, the PTA is determined for different PK/PD targets. Subsequently, the PK/PD target is plotted as a function of the MIC for the mean of the population and 95% and 99% CI estimates (corresponding to 97.5% and 99.5% PTA). EUCAST uses the MIC values resulting from both PTAs to determine a PK/PD breakpoint [21].

#### 4.3. Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring is the measurement of drug concentrations to optimize dosing regimens for individual patients with the objective to maximize efficacy and minimize toxicity [54]. Criteria for a drug to be appropriate for TDM are: large between-subject variability, small between-occasion variability, defined concentration-effect relationship, small therapeutic range, available analysis method and no clearly defined clinical parameter that allows dose adjustments (e.g. glucose or INR levels) [55].

##### 4.3.1. TDM approaches

TDM can be applied by evaluating whether the drug concentrations are in the therapeutic range, but in case of deviating concentrations, or when the therapeutic target is not just a concentration but e.g. an AUC, it is difficult to provide a dosing recommendation manually. A more robust approach to individualize dosing by TDM is the maximum a posteriori probability (MAP) Bayesian fitting procedure [30] (see 3.2.3), which is implemented in various TDM software programs [7,56] (see 4.3.2). The library of these TDM software tools include population parameters, SD's and covariates based on population PK models.

##### 4.3.2. TDM software programs

Several TDM computer tools are available. In 2012, a review of 12 software tools was published [56]; they differ in the number of drugs offered in the library (from 2 to 180). Eight of these programs provide the option to add new drug models. Other differences are the

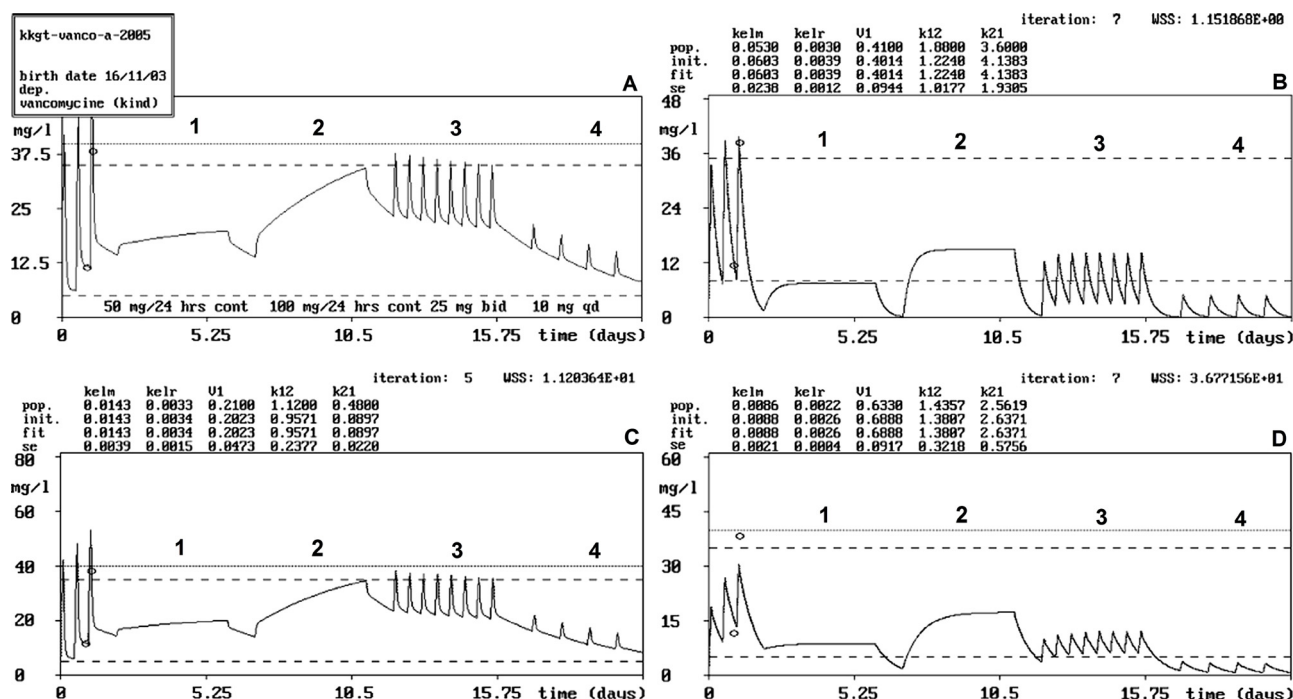


Fig. 5. TDM performance of 4 population models A–D (details displayed in Table 2) for 4 tested dosing regimens for each model: 1) 50 mg/24 h continuous infusion, 2) 100 mg/24 h continuous infusion, 3) 25 mg/12 h, 4) 10 mg/24 h. Reprinted with permission from *Therapeutic Drug Monitoring* [70].

availability of MAP Bayesian dosage adaptation (10/12 tools, see 3.2.3 for background information) and the proposal of a priori dosage regimens based on certain covariates (9/12 tools). The authors of the review recommend that most TDM software tools can be improved, more specifically the interface, user friendliness, data storage capability and report generation.

#### 4.3.3. TDM in clinical practice

TDM is applied to many antibiotic classes. For aminoglycosides (e.g. gentamicin, tobramycin and amikacin) and glycopeptides (e.g. vancomycin and teicoplanin), TDM has become standard clinical practice to balance efficacy and toxicity [57,58]. For other groups, such as beta-lactams and fluoroquinolones, TDM is not yet commonly employed [57,58]. The most important reasons that TDM is not commonly used for all antibiotic classes are unclear therapeutic targets (see 2.2.1), the lack of clinical outcome studies (4.3.4) and the unavailability of an assay in the hospital (4.3.6) [57–63].

#### 4.3.4. Challenge: clinical validation

Despite the fact that TDM is used extensively in clinical practice, there is a paucity of prospective studies on the influence of TDM on clinical outcomes [57,58,61–63]. Also for antibiotics which are already in TDM programs, prospective studies are sparse [54].

Examples of prospective studies are highlighted in the next paragraph 4.3.4.1.

**4.3.4.1. Examples: aminoglycosides, vancomycin, fluoroquinolones, beta-lactams.** Two prospective controlled studies about aminoglycoside TDM using Bayesian software showed that TDM significantly reduced nephrotoxicity, hospitalization and costs [64,65]. However, these two studies were performed before the introduction of extended-interval dosing of aminoglycosides and might not reflect the current practice.

For vancomycin, two prospective controlled studies showed that TDM significantly reduced nephrotoxicity [66,67].

A prospective controlled study including amikacin, ciprofloxacin, levofloxacin, ceftazidime and cefotaxime showed that TDM improved the probability of a good clinical outcome and pathogen eradication

[68]. In this study, Bayesian software was used only for amikacin and the two fluoroquinolones, but not for the two beta-lactams [68].

Another prospective beta-lactam TDM study didn't use Bayesian software to adjust dosing, but manually adjusted the frequency or infusion time [69]. Dosing was adjusted if the trough or steady state unbound concentration was below 4–5x MIC or above 10x MIC, which happened in 74.2% of the patients [69]. A main drawback of this study was the calculation of free concentrations using measured total concentrations and literature values for protein binding, while protein binding is often highly variable in critically ill patients [14]. Another limitation was the unavailability of MICs for a major part of the study population. By using ECOFFs (EUCAST epidemiological cut-off value) when a pathogen was isolated but no MIC available, or a MIC based on local epidemiology information of a potential pathogen (when no pathogen was isolated), a worst case scenario was applied and dosing adjustments might have been unnecessary [12]. In 2018, a prospective Dutch study evaluating a Bayesian TDM software program of beta-lactams will begin (the DIABOLO study, <https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004677-14/NL>).

#### 4.3.5. Challenge: population PK model selection

An important aspect of reliable TDM programs is the choice of a population PK model which must be suitable for the patient population for which TDM is performed.

Neef and colleagues presented a case of vancomycin MAP Bayesian adjustment where 4 different population PK models resulted in 4 strikingly different dosing schemes recommendations [70], see the example in 4.3.5.1 below.

Another study evaluated different population PK models for amikacin and also showed significant differences in model performance (results not shown here) [71].

**4.3.5.1. Example: vancomycin.** This case [70] describes a 3-week-old neonate (3.6 kg, 50 cm, serum creatinine 25  $\mu$ mol/L) receiving vancomycin 70 mg every 12 h with an infusion duration of 2 h. Two levels were drawn before and after the third dose. Fig. 5 shows the TDM performance of 4 models (presented in Table 2) for 4 tested dosing

**Table 2**  
PK models of vancomycin, used in the TDM software presented in Fig. 5 [70].

Model	Kelm (h <sup>-1</sup> )	Kelr (h <sup>-1</sup> (ml/min) <sup>-1</sup> )	V1 (L/kg)	K12 (h <sup>-1</sup> )	K21 (h <sup>-1</sup> )
A: Neonate < 15 PNA	0.457 ± 0.022	–	0.46 ± 0.23	1.5 ± 0.75	2.6 ± 1.3
B: Neonate > 15 PNA	0.053 ± 0.025	0.003 ± 0.021	0.41 ± 0.21	1.88 ± 1.21	3.6 ± 2.0
C: KKG T pop model	0.01429 ± 0.00286	0.00327 ± 0.00109	0.21 ± 0.042	1.12 ± 0.028	0.48 ± 0.12
D: Neonate AHZ	0.0086 ± 0.0009	0.0022 ± 0.0002	0.633 ± 0.060	1.4357 ± 0.1400	2.5619 ± 0.2500

Kelm: metabolic elimination rate constant, Kelr: renal elimination rate constant, V1: volume of distribution central compartment, K12: distribution rate constant from central to peripheral compartment, K21: distribution rate constant from peripheral to central compartment, PNA: postnatal age (days), KKG T: Dutch Association for Quality Assessment in TDM and Clinical Toxicology, AHZ: Central Pharmacy of The Hague Hospitals. Reprinted with permission from *Therapeutic Drug Monitoring* [70].

regimens. It is clear that model D has the worst fit of the measured levels. The other models have better fits, but model A predicts very high levels, probably due to absence of clearance in the model parameters. The conclusion of the authors is that model B best fit the data.

#### 4.3.6. Challenge: assay availability

Obviously, the availability of an assay is a limiting condition for TDM. However, the availability of assays differs per antibiotic and also per hospital. Most hospitals have assays for aminoglycosides and vancomycin [70], but assays for beta-lactams and fluoroquinolones are less common [10,13]. Possible reasons preventing institutions to provide TDM could be the absence of a prospective clinical outcome study or the requirement of a chromatographic method instead of an immunoassay [10].

#### 4.3.7. Challenge: MIC accuracy and variation

For dose adjustment of antibiotics based on TDM, both the measure of the concentration of the drug itself and the MIC of the pathogen responsible for the infection are necessary. However, most institutions use a single MIC determination which is inappropriate and can potentially cause underdosing of patients [12]. The accuracy and variation of MIC measurements must be carefully considered during this process [12].

## 5. Perspectives

The present review intended to provide background information on the current clinical applications of population PK modelling of antibiotics. There is an abundance of published population PK models which are used to evaluate dosing regimens, implemented in TDM software programs or used to set clinical breakpoints. These applications can be helpful to optimize the efficacy-toxicity balance of antibiotics, but have some limitations and knowledge gaps for which future research is needed.

### 5.1. PK/PD targets

More clarity about the optimal PK/PD target value of some antibiotics for specific clinical indications is required. Without a clear PK/PD target value, dosing recommendations from modelling and simulation studies are difficult to interpret and individualised dosing using TDM is hard to implement.

### 5.2. Assays

Obviously, an assay to measure antibiotic concentrations is essential to provide input for population PK models and to use them in clinical practise. It is important to measure unbound concentrations of antibiotics with a large variability in protein binding. Currently, assays for plasma concentrations are sufficient for clinical use because most current PK/PD target values are based on the concentrations in the central compartment, although the concentration at the infection site might also be important. Research on this topic is ongoing.

### 5.3. Population PK modelling and simulation

For reliable individual dosing recommendations in TDM programs as well as general dosing recommendations for specific patient groups, the choice of a population PK model suitable for that population is crucial. The used PTA acceptance levels in published dosing recommendations should be carefully considered.

PBPK (Physiologically Based PK) modelling methods [63] and joined clinical PK and PD modelling methods [61] are newer modelling methods which need to be further explored.

### 5.4. Clinical validation

It is imperative that the beneficial effects of dosing individualisation using TDM software be more prospectively studied. MIC accuracy and variation should be carefully considered during this process [12].

### 5.5. Interpretation of population PK modelling studies

Little knowledge of PK/PD and modelling prevents a good understanding of dosing recommendations resulting from modelling and simulation studies, clinical breakpoints and TDM. Therefore, good education on these topics is essential to improve antibiotic dosing in clinical practise.

## 6. Conclusions

Population PK models are extensively used in clinical practice to optimize antibiotic dosing. However, more clarity about PK/PD targets values, more clinical evaluation studies of model-based dosing recommendations and more clinical outcome studies of TDM are required.

### Conflicts of interest

J.W.M. has received research funding from IMI, the EU, ZON-MW, Adenium, Astra-Zeneca, Basilea, Eumedica, Cubist, Merck & Co, Pfizer, Polyphor, Roche, Shionogi, Thermo-Fisher, Wockhardt, Astellas, Gilead and Pfizer. All other authors: none to declare.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### References

- [1] J.W. Mouton, P.G. Ambrose, R. Canton, G.L. Drusano, S. Harbarth, A. MacGowan, et al., Conserving antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective, *Drug Resist Updat* 14 (2) (2011) 107–117, <https://doi.org/10.1016/j.drup.2011.02.005> PubMed PMID: 21440486.
- [2] European Medicines Agency, Guideline on the Use of Pharmacokinetics and Pharmacodynamics in the Development of Antimicrobial Medicinal Products,

- London (2016) [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2016/07/WC500210982.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500210982.pdf).
- [3] A.E. Muller, U. Theuretzbacher, J.W. Mouton, Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective, *Clin. Microbiol. Infect.* 21 (10) (2015) 881–885, <https://doi.org/10.1016/j.cmi.2015.06.007> PubMed PMID: 26093075.
- [4] M.A. Zeitlinger, H. Derendorf, J.W. Mouton, O. Cars, W.A. Craig, D. Andes, et al., Protein binding: do we ever learn? *Antimicrob. Agents Chemother.* 55 (7) (2011) 3067–3074, <https://doi.org/10.1128/AAC.01433-10> PubMed PMID: 21537013; PubMed Central PMCID: PMC3122431.
- [5] W.A. Craig, Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men, *Clin. Infect. Dis.* 26 (1) (1998) 1–10 PubMed PMID: 9455502.
- [6] M.J. Rybak, The pharmacokinetic and pharmacodynamic properties of vancomycin, *Clin. Infect. Dis.* 42 (Suppl. 1) (2006) S35–9, <https://doi.org/10.1086/491712> PubMed PMID: 16323118.
- [7] J.A. Roberts, M.H. Abdul-Aziz, J. Lipman, J.W. Mouton, A.A. Vinks, T.W. Felton, et al., Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions, *Lancet Infect. Dis.* 14 (6) (2014) 498–509, [https://doi.org/10.1016/S1473-3099\(14\)70036-2](https://doi.org/10.1016/S1473-3099(14)70036-2) PubMed PMID: 24768475; PubMed Central PMCID: PMC4181663.
- [8] P.G. Ambrose, S.M. Bhavnani, C.M. Rubino, A. Louie, T. Gumbo, A. Forrest, et al., Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore, *Clin. Infect. Dis.* 44 (1) (2007) 79–86, <https://doi.org/10.1086/510079> PubMed PMID: 17143821.
- [9] F.S. Sime, M.S. Roberts, S.L. Peake, J. Lipman, J.A. Roberts, Does Beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review, *Ann. Intensive Care* 2 (1) (2012) 35, <https://doi.org/10.1186/2110-5820-2-35> PubMed PMID: 22839761; PubMed Central PMCID: PMC3460787.
- [10] A. Huttner, S. Harbarth, W.W. Hope, J. Lipman, J.A. Roberts, Therapeutic drug monitoring of the beta-lactam antibiotics: what is the evidence and which patients should we be using it for? *J. Antimicrob. Chemother.* (2015), <https://doi.org/10.1093/jac/dkv201> PubMed PMID: 26188037.
- [11] M.G. Sinnolareddu, M.S. Roberts, J. Lipman, J.A. Roberts, Beta-lactam pharmacokinetics and pharmacodynamics in critically ill patients and strategies for dose optimization: a structured review, *Clin. Exp. Pharmacol. Physiol.* 39 (6) (2012) 489–496, <https://doi.org/10.1111/j.1440-1681.2012.05715.x> PubMed PMID: 22519600.
- [12] J.W. Mouton, A.E. Muller, R. Canton, C.G. Giske, G. Kahlmeter, J. Turnidge, MIC-based dose adjustment: facts and fables, *J. Antimicrob. Chemother.* (2017), <https://doi.org/10.1093/jac/dkx427> PubMed PMID: 29216348.
- [13] G. Wong, A. Brinkman, R.J. Benefield, M. Carlier, J.J. De Waele, N. El Helali, et al., An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units, *J. Antimicrob. Chemother.* 69 (5) (2014) 1416–1423, <https://doi.org/10.1093/jac/dkt523> PubMed PMID: 24443514.
- [14] G. Wong, S. Briscoe, S. Adnan, B. McWhinney, J. Ungerer, J. Lipman, et al., Protein binding of beta-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? *Antimicrob. Agents Chemother.* 57 (12) (2013) 6165–6170, <https://doi.org/10.1128/AAC.00951-13> PubMed PMID: 24480664; PubMed Central PMCID: PMC3837907.
- [15] K. Berthoin, E. Ampe, P.M. Tulkens, S. Carryn, Correlation between free and total vancomycin serum concentrations in patients treated for Gram-positive infections, *Int. J. Antimicrob. Agents* 34 (6) (2009) 555–560, <https://doi.org/10.1016/j.ijantimicag.2009.08.005> PubMed PMID: 19782538.
- [16] F. Scaglione, J.W. Mouton, R. Mattina, F. Fraschini, Pharmacodynamics of levofloxacin and ciprofloxacin in a murine pneumonia model: peak concentration/MIC versus area under the curve/MIC ratios, *Antimicrob. Agents Chemother.* 47 (9) (2003) 2749–2755 PubMed PMID: 12936969; PubMed Central PMCID: PMC3182632.
- [17] M. Schleibinger, C.L. Steinbach, C. Topper, A. Kratzer, U. Liebchen, F. Kees, et al., Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients, *Br. J. Clin. Pharmacol.* 80 (3) (2015) 525–533, <https://doi.org/10.1111/bcp.12636> PubMed PMID: 25808018; PubMed Central PMCID: PMC4574837.
- [18] K. Stoeckel, P.J. McNamara, R. Brandt, H. Plozza-Nottebrock, W.H. Ziegler, Effects of concentration-dependent plasma protein binding on ceftriaxone kinetics, *Clin. Pharmacol. Ther.* 29 (5) (1981) 650–657 PubMed PMID: 7053242.
- [19] J.W. Mouton, U. Theuretzbacher, W.A. Craig, P.M. Tulkens, H. Derendorf, O. Cars, Tissue concentrations: do we ever learn? *J. Antimicrob. Chemother.* 61 (2) (2008) 235–237, <https://doi.org/10.1093/jac/dkm476> PubMed PMID: 18065413.
- [20] M.P. Pai, D.T. Bearden, Antimicrobial dosing considerations in obese adult patients, *Pharmacotherapy* 27 (8) (2007) 1081–1091, <https://doi.org/10.1592/phco.27.8.1081> PubMed PMID: 17655508.
- [21] J.W. Mouton, D.F. Brown, P. Apfalter, R. Canton, C.G. Giske, M. Ivanova, et al., The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach, *Clin. Microbiol. Infect.* 18 (3) (2012) E37–45, <https://doi.org/10.1111/j.1469-0691.2011.03752.x> PubMed PMID: 22264314.
- [22] D.R. Mould, R.N. Upton, Basic concepts in population modeling, simulation, and model-based drug development, *CPT Pharm. Syst. Pharmacol.* 1 (2012) e6, <https://doi.org/10.1038/psp.2012.4> PubMed PMID: 23835886; PubMed Central PMCID: PMC3606044.
- [23] Y. Zhang, M. Huo, J. Zhou, S. Xie, PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in microsoft excel, *Comput. Methods Prog. Biomed.* 99 (3) (2010) 306–314, <https://doi.org/10.1016/j.cmpb.2010.01.007> PubMed PMID: 20176408.
- [24] D.R. Mould, R.N. Upton, Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods, *CPT Pharm. Syst. Pharmacol.* 2 (2013) e38, <https://doi.org/10.1038/psp.2013.14> PubMed PMID: 23887688; PubMed Central PMCID: PMC3636497.
- [25] C.M. Sherwin, T.K. Kiang, M.G. Spigarelli, M.H. Ensom, Fundamentals of population pharmacokinetic modelling: validation methods, *Clin. Pharmacokinet.* 51 (9) (2012) 573–590, <https://doi.org/10.2165/11634200-00000000-00000> PubMed PMID: 22799590.
- [26] T. Tatarinova, M. Neely, J. Bartroff, M. van Guilder, W. Yamada, D. Bayard, et al., Two general methods for population pharmacokinetic modeling: non-parametric adaptive grid and non-parametric Bayesian, *J. Pharmacokinet. Pharmacodyn.* 40 (2) (2013) 189–199, <https://doi.org/10.1007/s10928-013-9302-8> PubMed PMID: 23404393; PubMed Central PMCID: PMC3630269.
- [27] A. Racine-Poon, J. Wakefield, Statistical methods for population pharmacokinetic modelling, *Stat. Methods Med Res.* 7 (1) (1998) 63–84, <https://doi.org/10.1177/096228029800700106> PubMed PMID: 9533262.
- [28] X. Liu, Y. Wang, Comparing the performance of FOCE and different expectation-maximization methods in handling complex population physiologically-based pharmacokinetic models, *J. Pharmacokinet. Pharmacodyn.* 43 (4) (2016) 359–370, <https://doi.org/10.1007/s10928-016-9476-y> PubMed PMID: 27215925.
- [29] M.N. Neely, M.G. van Guilder, W.M. Yamada, A. Schumitzky, R.W. Jelliffe, Accurate detection of outliers and subpopulations with pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R, *Ther. Drug Monit.* 34 (4) (2012) 467–476, <https://doi.org/10.1097/FTD.0b013e31825c4ba6> PubMed PMID: 22722776; PubMed Central PMCID: PMC3394880.
- [30] R.W. Jelliffe, A. Schumitzky, D. Bayard, M. Milman, M. Van Guilder, X. Wang, et al., Model-based, goal-oriented, individualised drug therapy. Linkage of population modelling, new multiple model dosage design, bayesian feedback and individualised target goals, *Clin. Pharmacokinet.* 34 (1) (1998) 57–77, <https://doi.org/10.2165/00003088-199834010-00003> PubMed PMID: 9474473.
- [31] J.H. Proost, D.J. Eleveld, Performance of an iterative two-stage bayesian technique for population pharmacokinetic analysis of rich data sets, *Pharm. Res.* 23 (12) (2006) 2748–2759, <https://doi.org/10.1007/s11095-006-9116-0> PubMed PMID: 17089202.
- [32] C.C. Llanos-Paez, S. Hennig, C.E. Staatz, Population pharmacokinetic modelling, Monte carlo simulation and semi-mechanistic pharmacodynamic modelling as tools to personalize gentamicin therapy, *J. Antimicrob. Chemother.* 72 (3) (2017) 639–667, <https://doi.org/10.1093/jac/dkw461> PubMed PMID: 28062683.
- [33] J.A. Roberts, C.M. Kirkpatrick, J. Lipman, Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients, *J. Antimicrob. Chemother.* 66 (2) (2011) 227–231, <https://doi.org/10.1093/jac/dkq449> PubMed PMID: 21118912.
- [34] P.L. Bonate, A brief introduction to Monte Carlo simulation, *Clin. Pharmacokinet.* 40 (1) (2001) 15–22, <https://doi.org/10.2165/00003088-200140010-00002> PubMed PMID: 11236807.
- [35] F. de Velde, B.C. de Winter, B.C. Koch, T. van Gelder, J.W. Mouton, Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints, *J. Antimicrob. Chemother.* 71 (10) (2016) 2909–2917, <https://doi.org/10.1093/jac/dkw226> PubMed PMID: 27330071.
- [36] R. Jelliffe, M. Van Guilder, R. Leary, A. Schumitzky, X. Wang, A.A. Vinks, Nonlinear Parametric and Nonparametric Population Pharmacokinetic Modelling on a Supercomputer, Technical Report 99-1, University of Southern California, School of Medicine, Laboratory of Applied Pharmacokinetics, 1999, <http://www.lapok.org/pubsinfo/TechReports/TR99-1.pdf>.
- [37] C. Konig, S. Braune, J.A. Roberts, A. Nierhaus, O.M. Steinmetz, M. Baehr, et al., Population pharmacokinetics and dosing simulations of ceftazidime in critically ill patients receiving sustained low-efficiency dialysis, *J. Antimicrob. Chemother.* 72 (5) (2017) 1433–1440, <https://doi.org/10.1093/jac/dkw592> PubMed PMID: 28175308.
- [38] P.A. De Cock, H. Mulla, S. Desmet, F. De Somer, B.C. McWhinney, J.P. Ungerer, et al., Population pharmacokinetics of ceftazidime before, during and after cardiopulmonary bypass to optimize dosing regimens for children undergoing cardiac surgery, *J. Antimicrob. Chemother.* 72 (3) (2017) 791–800, <https://doi.org/10.1093/jac/dkw496> PubMed PMID: 27999040.
- [39] A.A. Udy, J. Lipman, P. Jarrett, K. Klein, S.C. Wallis, K. Patel, et al., Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? *Crit. Care* 19 (2015) 28, <https://doi.org/10.1186/s13054-015-0750-y> PubMed PMID: 25632974; PubMed Central PMCID: PMC4341874.
- [40] J.C. Bos, J.M. Prins, M.C. Misticio, G. Nunguiane, C.N. Lang, J.C. Beirao, et al., Pharmacokinetics and pharmacodynamic target attainment of ceftriaxone in adult severely ill sub-Saharan African patients: a population pharmacokinetic modelling study, *J. Antimicrob. Chemother.* (2018), <https://doi.org/10.1093/jac/dky071> PubMed PMID: 29522167.
- [41] K. Hui, K. Patel, D.C.M. Kong, C.M.J. Kirkpatrick, Impact of high-flux haemodialysis on the probability of target attainment for oral amoxicillin/clavulanic acid combination therapy, *Int. J. Antimicrob. Agents* (2017), <https://doi.org/10.1016/j.ijantimicag.2017.02.021> PubMed PMID: 28502697.
- [42] S. Goutelle, F. Valour, M.C. Gagnieu, F. Laurent, C. Chidiac, T. Ferry, et al., Population pharmacokinetics and probability of target attainment of erapenem administered by subcutaneous or intravenous route in patients with bone and joint infection, *J. Antimicrob. Chemother.* 73 (4) (2018) 987–994, <https://doi.org/10.1093/jac/dkx477> PubMed PMID: 29244077.
- [43] A. Smits, R.F. De Cock, K. Allegaert, S. Vanhaesebrouck, M. Danhof, C.A. Knibbe, Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice, *Antimicrob. Agents Chemother.* 59 (10) (2015) 6344–6351, <https://doi.org/10.1128/AAC.01157-15> PubMed PMID:



- 26248375; PubMed Central PMCID: PMC4576045.
- [44] P.G. Ambrose, S.M. Bhavnani, R.C. Owens Jr, Clinical pharmacodynamics of quinolones, *Infect. Dis. Clin. North Am.* 17 (3) (2003) 529–543 PubMed PMID: 14711075.
- [45] K.J. Madaras-Kelly, B.E. Ostergaard, L.B. Hovde, J.C. Rotschafer, Twenty-four-hour area under the concentration-time curve/MIC ratio as a generic predictor of fluoroquinolone antimicrobial effect by using three strains of *Pseudomonas aeruginosa* and an in vitro pharmacodynamic model, *Antimicrob. Agents Chemother.* 40 (3) (1996) 627–632 PubMed PMID: 8851583; PubMed Central PMCID: PMC163170.
- [46] A. Forrest, D.E. Nix, C.H. Ballow, T.F. Goss, M.C. Birmingham, J.J. Schentag, Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients, *Antimicrob. Agents Chemother.* 37 (5) (1993) 1073–1081 PubMed PMID: 8517694; PubMed Central PMCID: PMC187901.
- [47] Bayer, Prescribing Information Cipro IV (R) (Ciprofloxacin) Injection, for Intravenous Use, (2016).
- [48] Kabi Fresenius, Summary of Product Characteristics: Ciprofloxacin for Infusion, (2017).
- [49] A.R. van Zanten, K.H. Polderman, I.M. van Geijlswijk, G.Y. van der Meer, M.A. Schouten, A.R. Girbes, Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study, *J. Crit. Care* 23 (3) (2008) 422–430, <https://doi.org/10.1016/j.jcrrc.2007.11.011> PubMed PMID: 18725050.
- [50] S. Zelenitsky, R. Ariano, G. Harding, A. Forrest, Evaluating ciprofloxacin dosing for pseudomonas aeruginosa infection by using clinical outcome-based Monte Carlo simulations, *Antimicrob. Agents Chemother.* 49 (10) (2005) 4009–4014, <https://doi.org/10.1128/AAC.49.10.4009-4014.2005> PubMed PMID: 16189073; PubMed Central PMCID: PMC1251501.
- [51] D. Khachman, J.M. Conil, B. Georges, S. Saivin, G. Houin, P.L. Toutain, et al., Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population pharmacokinetic-pharmacodynamic analysis and Monte Carlo simulations, *J. Antimicrob. Chemother.* 66 (8) (2011) 1798–1809, <https://doi.org/10.1093/jac/dkr220> PubMed PMID: 21653603.
- [52] M. Haeseker, L. Stolk, F. Nieman, C. Hoebe, C. Neef, C. Bruggeman, et al., The ciprofloxacin target AUC : MIC ratio is not reached in hospitalized patients with the recommended dosing regimens, *Br. J. Clin. Pharmacol.* 75 (1) (2013) 180–185, <https://doi.org/10.1111/j.1365-2125.2012.04337.x> PubMed PMID: 22616681; PubMed Central PMCID: PMC3555057.
- [53] European Medicines Agency, Ciprofloxacin Bayer, Article 30 referral (2008) [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referrals\\_document/Ciprofloxacin\\_Bayer\\_30/WC500008075.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Ciprofloxacin_Bayer_30/WC500008075.pdf).
- [54] D.J. Touw, C. Neef, A.H. Thomson, A.A. Vinks, Cost-effectiveness of therapeutic drug monitoring committee of the International association for therapeutic drug M, clinical T. Cost-effectiveness of therapeutic drug monitoring: a systematic review, *Ther. Drug Monit.* 27 (1) (2005) 10–17 PubMed PMID: 15665740.
- [55] M.H. Ensom, G.A. Davis, C.D. Cropp, R.J. Ensom, Clinical pharmacokinetics in the 21st century. Does the evidence support definitive outcomes? *Clin. Pharmacokinet.* 34 (4) (1998) 265–279, <https://doi.org/10.2165/00003088-199834040-00001> PubMed PMID: 9571300.
- [56] A. Fuchs, C. Csajka, Y. Thoma, T. Buclin, N. Widmer, Benchmarking therapeutic drug monitoring software: a review of available computer tools, *Clin. Pharmacokinet.* 52 (1) (2013) 9–22, <https://doi.org/10.1007/s40262-012-0020-y> PubMed PMID: 23196713.
- [57] J.A. Roberts, R. Norris, D.L. Paterson, J.H. Martin, Therapeutic drug monitoring of antimicrobials, *Br. J. Clin. Pharmacol.* 73 (1) (2012) 27–36, <https://doi.org/10.1111/j.1365-2125.2011.04080.x> PubMed PMID: 21831196; PubMed Central PMCID: PMC3248253.
- [58] G. Wong, F.B. Sime, J. Lipman, J.A. Roberts, How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? *BMC Infect. Dis.* 14 (2014) 288, <https://doi.org/10.1186/1471-2334-14-288> PubMed PMID: 25430961; PubMed Central PMCID: PMC4289211.
- [59] N.G. Jager, R.M. van Hest, J. Lipman, F.S. Taccone, J.A. Roberts, Therapeutic drug monitoring of anti-infective agents in critically ill patients, *Expert Rev. Clin. Pharmacol.* 9 (7) (2016) 961–979, <https://doi.org/10.1586/17512433.2016.1172209> PubMed PMID: 27018631.
- [60] F.B. Sime, M.S. Roberts, J.A. Roberts, Optimization of dosing regimens and dosing in special populations, *Clin. Microbiol. Infect.* 21 (10) (2015) 886–893, <https://doi.org/10.1016/j.cmi.2015.05.002> PubMed PMID: 25980350.
- [61] T. Tangden, V. Ramos Martin, T.W. Felton, E.I. Nielsen, S. Marchand, R.J. Bruggemann, et al., The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections, *Intensive Care Med.* 43 (7) (2017) 1021–1032, <https://doi.org/10.1007/s00134-017-4780-6> PubMed PMID: 28409203.
- [62] M. Neely, Scalpels not hammers: the way forward for precision drug prescription, *Clin. Pharmacol. Ther.* (2016), <https://doi.org/10.1002/cpt.593> PubMed PMID: 27984653.
- [63] A.S. Darwich, K. Ogungbenro, A.A. Vinks, J.R. Powell, J.L. Reny, N. Marsousi, et al., Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future, *Clin. Pharmacol. Ther.* (2017), <https://doi.org/10.1002/cpt.659> PubMed PMID: 28182269.
- [64] N.A. van Lent-Evers, R.A. Mathot, W.P. Geus, B.A. van Hout, A.A. Vinks, Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis, *Ther. Drug Monit.* 21 (1) (1999) 63–73 PubMed PMID: 10051056.
- [65] C.J. Destache, S.K. Meyer, M.J. Bittner, K.G. Hermann, Impact of a clinical pharmacokinetic service on patients treated with aminoglycosides: a cost-benefit analysis, *Ther. Drug Monit.* 12 (5) (1990) 419–426 PubMed PMID: 2127324.
- [66] M.D. Fernandez de Gatta, M.V. Calvo, J.M. Hernandez, D. Caballero, J.F. San Miguel, A. Dominguez-Gil, Cost-effectiveness analysis of serum vancomycin concentration monitoring in patients with hematologic malignancies, *Clin. Pharmacol. Ther.* 60 (3) (1996) 332–340, [https://doi.org/10.1016/S0009-9236\(96\)90060-0](https://doi.org/10.1016/S0009-9236(96)90060-0) PubMed PMID: 8841156.
- [67] T.E. Welty, A.K. Copa, Impact of vancomycin therapeutic drug monitoring on patient care, *Ann. Pharmacother.* 28 (12) (1994) 1335–1339, <https://doi.org/10.1177/106002809402801201> PubMed PMID: 7696720.
- [68] F. Scaglione, S. Esposito, S. Leone, V. Lucini, M. Pannacci, L. Ma, et al., Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia, *Eur. Respir. J.* 34 (2) (2009) 394–400, <https://doi.org/10.1183/09031936.00149508> PubMed PMID: 19213786.
- [69] J.A. Roberts, M. Uildemolins, M.S. Roberts, B. McWhinney, J. Ungerer, D.L. Paterson, et al., Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept, *Int. J. Antimicrob. Agents.* 36 (4) (2010) 332–339, <https://doi.org/10.1016/j.ijantimicag.2010.06.008> PubMed PMID: 20685085.
- [70] C. Neef, D.J. Touw, A.R. Hartevelde, J.J. Eerland, D.R. Uges, Pitfalls in TDM of antibiotic drugs: analytical and modelling issues, *Ther. Drug Monit.* 28 (5) (2006) 686–689, <https://doi.org/10.1097/01.ftd.0000243966.97964.11> PubMed PMID: 17038886.
- [71] M.D. Mar Fernandez de Gatta, M. Victoria Calvo, R. Ardanuy, A. Dominguez-Gil, J.M. Lanao, S.R. Moreno, Evaluation of population pharmacokinetic models for amikacin dosage individualization in critically ill patients, *J. Pharm. Pharmacol.* 61 (6) (2009) 759–766, <https://doi.org/10.1211/jpp/61.06.0008> PubMed PMID: 19505366.