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Review

What Are the Current Approaches to Optimising Antimicrobial Dosing in the Intensive Care Unit?

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Abstract: Antimicrobial dosing in the intensive care unit (ICU) can be problematic due to various challenges including unique physiological changes observed in critically ill patients and the presence of pathogens with reduced susceptibility. These challenges result in reduced likelihood of standard antimicrobial dosing regimens achieving target exposures associated with optimal patient outcomes. Therefore, the aim of this review is to explore the various methods for optimisation of antimicrobial dosing in ICU patients. Dosing nomograms developed from pharmacokinetic/statistical models and therapeutic drug monitoring are commonly used. However, recent advances in mathematical and statistical modelling have resulted in the development of novel dosing software that utilise Bayesian forecasting and/or artificial intelligence. These programs utilise therapeutic drug monitoring results to further personalise antimicrobial therapy based on each patient's clinical characteristics. Studies quantifying the clinical and cost benefits associated with dosing software are required before widespread use as a point-of-care system can be justified.

Keywords: nomogram; software; antimicrobials; critical illness; pharmacokinetics; Bayesian forecasting; sepsis; artificial intelligence

1. Introduction

Sepsis is a leading source of morbidity and mortality among critically ill patients in the intensive care unit (ICU) [1–3]. In addition to selecting the most appropriate antimicrobial agent, there is increasing awareness of how dosing strategies employed can have profound implications on the success of therapy in this patient group [4,5]. Suboptimal antimicrobial dosing reduces the likelihood of achieving pharmacokinetic-pharmacodynamic (PK-PD) targets needed for therapeutic success. With an increasing appreciation of the importance of achieving these PK-PD targets, regulatory bodies are progressively incorporating the use of PK-PD studies through pharmacometrics as part of their regulatory assessment of new antimicrobials and their licensed doses [6]. Critically ill patients, in particular, are at an increased risk of treatment failure due to the unique physiological changes commonly seen in these patients and the interventions they are exposed to that often result in alterations to antimicrobial PK and achievement of PK-PD targets.

1.1. Altered Pharmacokinetics

Traditionally, drug dosing takes a "one-size-fits-all" approach whereby pharmacokinetic (PK) data is used to define dosing regimens to be used in indications for which the drug is licensed. This PK data predicts the likely drug exposure that can be obtained from a chosen antimicrobial dosing regimen [7]. As these studies are typically conducted in healthy volunteers and not severely unwell patients, extrapolating these dosing recommendations to other patient groups does not account for altered PK that is often observed in this such populations, especially in the critically ill [8].

A common finding in critically ill patients with sepsis is the presence of large fluid shifts (or the third-spacing phenomenon) into the interstitial space, which can alter antimicrobial exposure by increasing their volume of distribution. Through movement of drug into this additional compartment, there is less drug available in plasma and potentially at the site of infection [9], reducing the likelihood of optimal drug exposure and patient outcomes [10]. Hydrophilic antimicrobials, such as aminoglycosides and beta-lactams, are more affected by this fluid redistribution than lipophilic antimicrobials [11]. Other physiological changes seen in sepsis include the presence of organ dysfunction. Given that the hepatic [12–14] and renal systems [15–18] are responsible for metabolism and excretion of many antimicrobial agents, derangements in function are likely to result in drug accumulation. If antimicrobial dosing is not adapted to organ dysfunction, drug-related toxicity from high drug exposures may result [19,20].

Alternatively, increased cardiac output from sepsis and inotrope/vasopressor use have been shown to increase renal perfusion and induce augmented renal clearance (ARC, defined as a glomerular filtration rate above 130 mL/min/1.73 m^2 [21]). ARC can dramatically increase the clearance of renally-cleared hydrophilic antimicrobials [22,23]. Reduction in plasma albumin concentrations is common in critically ill patients which can increase clearance of highly protein-bound antimicrobials (and reduced concentrations), for example, ceftriaxone and teicoplanin, as there is an increase in free drug available for clearance [24]. These collective physiological changes have been shown to reduce the likelihood of achieving exposure targets needed for antimicrobial efficacy and potentially increasing the risk of treatment failure [10,19,25–28].

An additional level of complexity to antimicrobial dosing in critically ill patients stems from the treatments used to support failing organs. Extracorporeal interventions such as extracorporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT), although lifesaving, can profoundly alter antimicrobial exposure in these patients. Adult patients exposed to ECMO can have further increases in the volume of distribution of highly protein-bound and/or lipophilic antimicrobials through sequestration onto the ECMO circuits [29–31]. Compared to non-dialysed patients with renal failure, patients receiving RRT may exhibit significant clearances of hydrophilic antimicrobials through losses in the ultrafiltrate and dialysate [32]. With both interventions, the impact of drug clearance or distribution is affected by a wide variety of extracorporeal parameters including the type of material used for the oxygenator or filter and their surface areas, blood and effluent flow rates, configuration or modality of the intervention used as well as replacement fluid settings, especially for RRT. Hence, these interventions make it difficult to predict resulting antimicrobial exposure given the large variations in extracorporeal parameters used in clinical settings. If ECMO and/or RRT are unaccounted for with the dosing regimen selected, this may lead to treatment failure or drug toxicity. Collectively, optimising antimicrobial therapy in this patient group is critical to ensure positive patient outcomes as these patients are often the sickest cohort in the ICU [33–37].

1.2. Pharmacodynamic Considerations

Another major factor that impacts on treatment success is the pharmacodynamics (PD) of an antimicrobial. PK-PD describes the optimum unbound exposure to an antimicrobial agent that is needed for treatment success and is influenced by the primary PD parameter, the minimum inhibitory concentration (MIC) [38]. The MIC is an in vitro measurement that describes the susceptibility of an organism to an antimicrobial agent and hence affects the exposure required for antimicrobial efficacy.

Examples of PK-PD indices used to measure antimicrobial efficacy include the ratio of the area under the curve of the unbound drug (AUC) to the MIC (fAUC$_{0–24}$/MIC; where f denotes free, or unbound exposure), the ratio of the maximal unbound drug concentration to the MIC (fC$_{max}$/MIC) and the cumulative percentage of a dosing interval that the antimicrobial concentration exceeds the MIC (%fT > MIC) [39]. Although not all PK-PD indices in studies are described according to the unbound concentration (only total concentration may be measured), it is the unbound concentration of drug that is responsible for antimicrobial effect. Table 1 shows the PK-PD indices used to describe microbial kill characteristics of commonly used antimicrobial agents.

Table 1. List of commonly used antimicrobial classes and their pharmacokinetic-pharmacodynamic (PK-PD) indices.

Class	PK-PD Index	Reference
Aminoglycosides	Cmax/MIC AUC$_{0–24}$/MIC	[40]
Beta-Lactams	fT > MIC	[41]
Fluoroquinolones	Cmax/MIC AUC$_{0–24}$/MIC	[33,42]
Glycopeptides	AUC$_{0–24}$/MIC	[43]
Glycylcyclines	AUC$_{0–24}$/MIC	[44,45]
Lincosamides	fT > MIC	[46]
Lipopeptides	Cmax/MIC AUC$_{0–24}$/MIC	[47]
Macrolides	fT > MIC AUC$_{0–24}$/MIC (azithromycin)	[48,49]
Oxazolidinones	fT > MIC AUC$_{0–24}$/MIC	[50]
Polymyxins	AUC$_{0–24}$/MIC	[51]
Triazoles antifungals	AUC$_{0–24}$/MIC	[52]
Echinocandins	AUC$_{0–24}$/MIC Cmax/MIC	[53]
Polyenes	Cmax/MIC	[54]

Pathogens isolated in critically ill patients often exhibit higher MICs compared to those isolated among ward-based patients [55–61]. This may mean that higher antimicrobial exposures are needed to attain PK-PD targets associated with optimal clinical outcome. Together with the altered PK observed in these patients, these scenarios are very challenging when faced by ICU clinicians [62]. Furthermore, sub-optimal therapy carries an increased risk of developing antimicrobial-resistant pathogens which has negative consequences in patients both in and outside of the ICU [63].

The pathogen's MIC can influence the antimicrobial exposure required to achieve a PK-PD target as it acts as the denominator in each index. The MIC should be interpreted in the context of the microbiological susceptibility testing method used (such broth microdilution versus E-test), the pathogen identified and its wild-type distribution. However, it is important to note that the measurement process of MICs is susceptible to laboratory assay and microbiological sample variations [38]. This may inadvertently result in the MIC being reported incorrectly by one to two dilutions and this can affect the achievement of appropriate PD targets, although the clinical outcome implications of MIC measurement error remain uncertain.

Collectively, the dynamic interplay between PK and PD demonstrates how antimicrobial exposure impacts on the critical care patient (Figure 1). Clinicians should adopt a PK-PD based approach to dosing in order to avoid the risks of sub-optimal exposure associated with using standard antimicrobial doses.

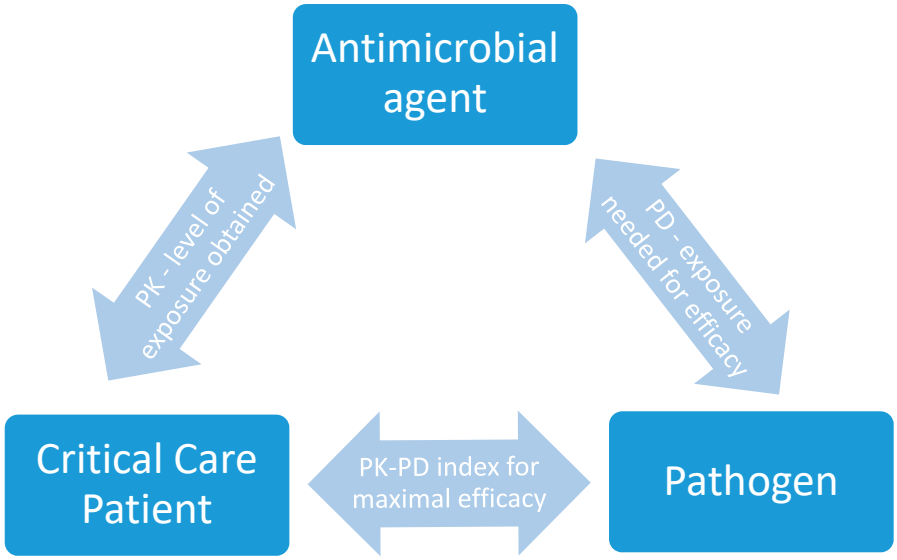

Figure 1. Dynamic interplay between the critical care patient, antimicrobial agent of choice, and the pathogen.

The purpose of this review is to describe tools currently available to assist clinicians to achieve therapeutic PK-PD targets by individualising dosing. These include use of dosing nomograms, therapeutic drug monitoring, and dosing software where each tool can function individually or in conjunction with each other to optimise the dosing of antimicrobials (see Figure 2).

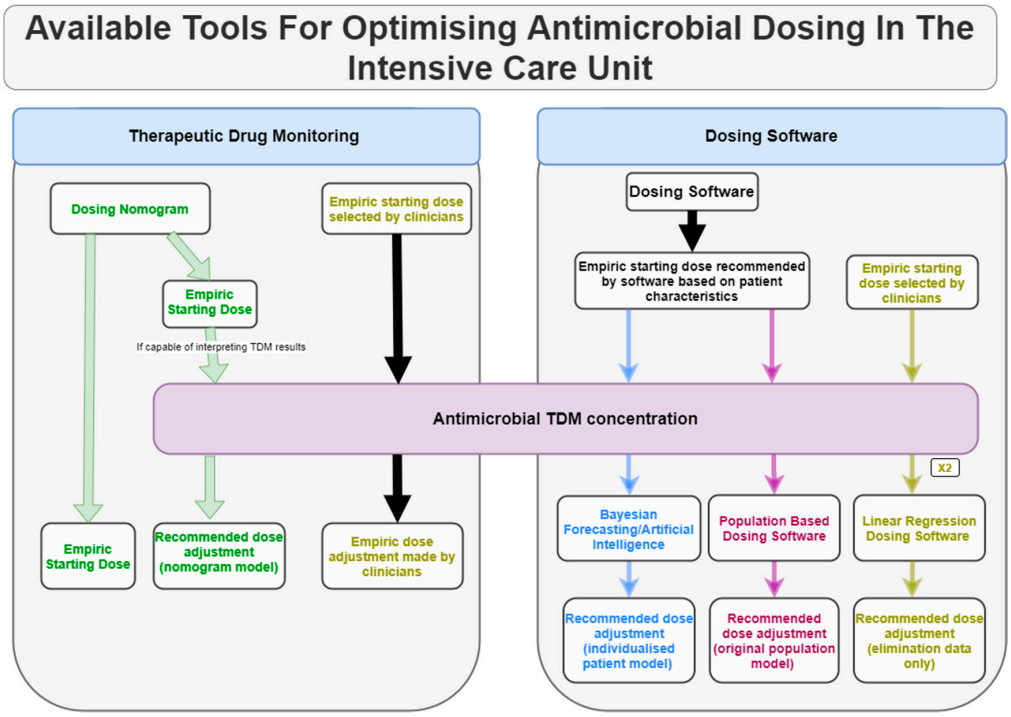

Figure 2. Range of available tools to assist clinicians with optimising the dosing of antimicrobials in the intensive care unit (ICU). Simple applications such as dosing nomograms and therapeutic drug monitoring (TDM) provide clinicians with basic tools needed to improve probability of achieving PK-PD targets and determine if they have been successfully achieved. Computerised programs such as dosing software (and some nomograms) are able to utilise antimicrobial TDM results to generate refined recommendations based on the model underpinning the software.

2. Dosing Nomograms

A simple but systematic approach to guide dosing of antimicrobials is the use of dosing nomograms. This is one of the most common approaches taken in non-critical care settings whereby doses are based on patient characteristics (typically renal function or weight) or antimicrobial plasma concentrations, if available [64]. Nomograms are developed from PK studies or statistical analyses (such as multiple linear regression models) in the population of interest and seek to describe the dose-concentration relationship of an antimicrobial. From these data, a model is generated that then will underpin the dosing recommendations of the nomogram using relevant patient characteristics [65]. Based on patient characteristics, an individualised starting dose likely to achieve the nominated PK-PD targets can be generated from the dosing nomogram. Additionally, some nomograms have the ability to generate subsequent dosage adjustment recommendations using resulting antimicrobial plasma concentrations if available [66].

Compared to clinician-guided dosing alone, use of dosing nomograms in the ICU has shown some promise. For example, an improvement in target attainment of vancomycin plasma concentrations (defined in this study as a trough concentration between 20–30 mg/L) was seen within the first day of treatment with 84% of patients achieving therapeutic concentrations when a dosing nomogram was used compared to 51% of patients when dosed empirically by clinicians [67]. Other nomograms for antimicrobial drugs in the ICU population have also been described for vancomycin [68–71], gentamicin [72] and meropenem [73].

A limitation to using dosing nomograms in the ICU is its ability to consider only one or two patient characteristics at a time, with additional inputs complicating the feasibility of a nomogram and impair usability. This reduces the clinician's ability to include more data such as pathogen-specific information to further individualise the dosing recommendations of the nomogram. The dosing recommendations from these nomograms are typically aimed at achieving pre-defined PK targets [66,74] which may not be universally applicable to all ICU patients, given that some patients may be infected with pathogens with higher MICs.

In spite of the limitations described, nomograms may still be a useful tool for improving antimicrobial dosing to help achieve PK-PD targets when compared to empiric dosing regimens selected by clinicians alone. The use of nomograms generally does not require significant changes to pre-existing infrastructure (such as new assays for measuring antimicrobial concentrations) beyond clinician education which may make implementation easier, even in ICUs with more limited resources such as those in low and middle income countries.

3. Therapeutic Drug Monitoring in the Intensive Care Unit (ICU)

The use of therapeutic drug monitoring (TDM) represents one of the earliest forms of personalising antimicrobial therapy/dosing [75]. TDM was traditionally used to ensure that patients receiving antimicrobials with a narrow therapeutic index were not exposed to toxic exposures associated with serious side effects. Examples of antimicrobials that were targeted for this purpose include aminoglycosides and glycopeptides where the risk of nephro- and oto-toxicity is higher than for other antimicrobials [76]. With an increasing appreciation of how achieving PK-PD targets increases the likelihood of treatment success, TDM has now expanded to include optimising antimicrobial exposure to increase the likelihood of clinical and microbiological cure, as well as, minimise drug toxicity.

At its simplest, TDM entails obtaining a plasma drug concentration during a course of antimicrobial therapy. This concentration is interpreted by the clinician to be either therapeutic or not therapeutic, in which case the clinician will adjust the dosing regimen by a magnitude that they anticipate will achieve a predefined PK-PD target. Although use of TDM has been shown to increase the proportion of patients who achieve PK-PD targets of antimicrobials compared to empiric dosing by clinicians alone [77], it is prone to significant inter-clinician variability in dosing recommendation selected [78]. This may reduce the consistency of achieving these PK-PD targets when dosing is led by different clinicians. Furthermore, variability between countries and healthcare networks with

respect to their TDM practices and availability may increase variability in dosing recommendations across institutions [79,80]. Importantly, dosing changes may be more challenging in antimicrobials where exposures can be influenced by multiple factors such as renal function and plasma protein binding. To circumvent these hurdles, TDM results can be integrated with other tools such as dosing nomograms and/or software to help improve the likelihood that revised doses will achieve predefined PK-PD targets.

There are several considerations clinicians should be aware of when employing TDM, including the availability of appropriate assays needed to generate the TDM results [81]. Not all ICUs have access to these assays which may explain the variability across ICUs in antimicrobials that are actively monitored using this process [79]. Furthermore, the majority of data and suggested reference ranges are based on concentrations obtained from blood (or plasma). These antimicrobial concentrations do not always reflect concentrations at the site of infection (e.g., pulmonary epithelial lining fluid for pneumonia or cerebrospinal fluid for meningitis) [82]. Although preliminary studies have attempted to generate models that predict the antimicrobial concentrations at the site of infection from blood plasma concentrations, their predictive performance has been generally poor [83,84]. For an antimicrobial to reach the site of infection, it must partition out of circulation, diffuse through the interstitial fluid and finally pass into the tissue of interest [85]. Depending on the location of this tissue, a wide variety of factors can influence penetration into the infective site. Examples include drug-specific parameters such as degree of protein binding and physicochemical properties of the drug as well as tissue properties which may include the presence of occluding tissue borders (such as the blood-brain barrier) or membrane transporters (which can enhance or hinder the transport of antimicrobials to and from the site of infection) [85]. In these clinical scenarios, plasma concentrations act as surrogate markers as sampling at the clinical site of infection through procedures such as bronchoalveolar lavage in pneumonia or lumbar puncture in central nervous system (CNS) infections can often be impractical or too invasive to be conducted on a routine basis.

Given this, clinicians may choose to aim for higher plasma concentrations to create a larger concentration gradient with tissues to drive the antimicrobial into the site of infection if a drug is known to have variable penetration. Vancomycin for treating CNS infections is a common example whereby in practice trough concentrations are targeted up to 20–25 mg/L (as opposed to 15–20 mg/L for other infections) due to reduced penetration across the blood-brain barrier which may also be variable depending on the degree of meningeal inflammation [86]. Further studies are needed in this area to better define plasma exposure targets of antimicrobials that best correlate with optimal tissue concentrations and patient outcomes.

Additionally, as only the unbound drug is pharmacologically active to exert a therapeutic effect, highly protein-bound antimicrobial agents (usually clinically significant when more than 70% of the drug is protein bound [87]) warrant additional considerations given the reduction in protein concentrations commonly seen in critically ill patients. Plasma concentrations are typically reported as 'total' drug concentrations as measuring only the unbound concentration is more onerous and expensive [88]. However, in ICU patients, measuring total plasma concentrations may not provide an accurate reflection of the unbound concentration needed to achieve PK-PD targets. Previous studies have demonstrated that highly protein-bound antimicrobials such as ceftriaxone and flucloxacillin have poor correlations between their total and unbound concentrations, making it difficult to predict if appropriate target unbound exposures have been achieved when only total concentrations are measured [89]. In patients prescribed drugs with high and/or variable protein binding, adjusting antimicrobial regimens based on total concentrations may result in inaccurate PK-PD target attainment and unbound concentrations should be measured if available. Assays validated to measure the unbound concentration of various antimicrobials have been developed [88].

4. Dosing Software

With advances in the ability of computers to perform complex mathematical modelling and statistical analysis, clinicians have access to integrate PK models and/or pharmaco-statistical outputs that have been embedded into dosing software to assist with drug dosing. Depending on the model underpinning the program, dosing software can be broadly divided into a system that utilises (a) linear regression models, (b) population PK models, and/or (c) models that incorporate Bayesian forecasting or artificial intelligence.

The benefits of using dosing software when compared with dosing nomograms or standard TDM processes include simplification of the process of calculating complex PK-PD parameters (such as AUC/MIC ratios). These PK-PD indices are being increasingly used in clinical practice to determine appropriate antimicrobial exposure targets. Measurement of surrogate targets, such as trough concentrations, may be alternatives in the absence of dosing software. However, as evidenced by vancomycin, target trough concentrations inconsistently correlate with the actual AUC/MIC targets for clinical efficacy, thereby risking drug toxicity [90].

Below is a brief description of the different approaches currently available for dosing software programs.

4.1. Linear Regression Based Dosing Software

A simpler form of dosing software is based on linear regression principles whereby two plasma concentrations at different time points are obtained and an algorithm calculates a drug clearance rate. This can then be used to calculate a dose adjustment regimen. Aminoglycoside dose optimisation with the program Aminoglycoside Levels and Daily Dose Indicator (ALADDIN) is one such example of this [91,92]. Outside of the ICU, the use of this program has been shown to produce dosing recommendations that are different from dosing nomograms but the predictive performance in terms of PK-PD target attainment have yet to be quantified. Interestingly, the use of ALADDIN may be associated with a lower incidence of nephrotoxicity compared to dosing with nomograms [92]. This potentially suggests linear regression dosing software may be superior to simpler methods such as dosing nomograms for dosing aminoglycosides, but this has yet to be prospectively examined in the ICU cohort.

As linear regression programs do not include population PK models, multiple samples of measured plasma concentrations are required in order to describe an individual PK profile [65]. These programs are unable to generate empiric starting doses based on patient covariates and do not consider any other patient data in their analysis and recommendations. As each set of concentrations are analysed individually, these programs do not have the ability to consider previous TDM results for the patient to further refine the accuracy of dosing recommendations, which may be necessary in the event of changes in a patient's clinical condition. Collectively, this may impair a clinician's ability to make the most accurate dosing recommendations in a timely fashion.

4.2. Population PK-Based Dosing Software

Dosing software programs that utilise population PK or statistical models could be considered advanced dosing nomograms. Patient covariates, or measured drug concentrations, are entered into the software and the program generates a starting dose recommendation or dosage adjustment, that aims to achieve a predefined antimicrobial exposure [93]. Unlike linear regression-based programs, population PK based models are effective with even one plasma concentration measurement as the program is able to utilise the underlying model to predict the necessary dose alterations needed to achieve a PK-PD target [92]. Accuracy typically improves if a second (or third) plasma concentration is included.

Thus far, population PK-based dosing software has shown some promise. For example, the program DoseCalc produced similar dosing recommendations to clinicians who performed complex manual calculations for aminoglycosides dosing when targeting an $AUC_{0–24}$/MIC target [93].

The software also generated recommendations that were closer to manually calculated doses compared to a dosing nomogram when used in patients with renal dysfunction. Unfortunately, predictive performance using measured plasma concentrations was not evaluated.

One limitation associated with using population PK-based methods is the inability to use measured antimicrobial concentrations from the patient to further individualise the model (i.e., *a posteriori* PK parameter estimates) [94,95]. This may reduce the potential predictive accuracy of the program when new dosing recommendations are required in the event there is a change in a patient's clinical parameters without obtaining further TDM concentrations. Hence, recommendations are extrapolated from the population PK model driving the software, not the individual patient's PK parameters, which may potentially delay achievement of PK-PD targets. Additionally, many population PK model softwares do not contain models from critical care patients which may compromise accuracy when used in the critical care cohort [5].

4.3. Bayesian Forecasting Dosing Software

Software that utilises Bayesian forecasting typically uses population PK data to estimate a recommended dose that is likely to help achieve a predefined PK-PD target. However, Bayesian forecasting has the added benefit of using data (such as TDM results) to generate *a posteriori* PK parameter estimates that can strengthen and improve the accuracy of future dosing recommendations (Figure 3) [96]. They also have the ability to account for pathogen-specific parameters such as MIC where variations in the degree of susceptibility will alter the dosing regimens that are needed to achieve the PK-PD targets. In this way, Bayesian forecasting is able to account for any patient variations from the population that the initial PK model was built on. Similar to population PK based methods, Bayesian forecasting removes the need for multiple drug samplings as the program is able to utilise population PK data to predict likely antimicrobial concentrations and generate dosing requirements needed to achieve the PK-PD targets [97].

The use of Bayesian methods for optimising drug dosing was first described in the 1970s but required complex mathematical calculations that most clinicians were unlikely to be familiar with [98]. Combined with the lack of awareness then around the PK differences in patient populations and its impact on achieving antimicrobial PK-PD targets, this likely may have led to poor uptake amongst clinicians. It was not until advances with computer sciences that enabled dosing software to integrate Bayesian forecasting into the analysis were clinicians able to appreciate the potential benefits of using it to help optimise antimicrobial treatment in the critical care patient group. Examples of dosing software with Bayesian forecasting include but are not exclusive to Best Dose, ID-ODS, DoseMe, and TCI Works [5]. Some of these programs include population PK models for antimicrobials specific to the critically ill patients with sepsis built into the dosing software. Details of antimicrobial population PK models developed from critical care patient groups are provided in Appendix A.

To date, there are limited studies prospectively evaluating the performance of Bayesian dosing software in the ICU. In one prospective study involving critical care patients using cefepime, meropenem and piperacillin-tazobactam, the use of the dosing software ID-ODS resulted in 98% of patients achieving the predefined PK-PD target of time above MIC of the dosing interval (50% for piperacillin, 40% for meropenem and 60% for cefepime) [99]. Though there were no control groups to compare target attainment in the absence of dosing software, 22% of dosing software optimised patients received a different dose to standard doses that would have been used in the study ICU, which raises the possibility of inadequate or excessive antimicrobial exposure in those patients if standard doses were used, although MICs were generally low. Studies demonstrating positive clinical outcomes associated with attainment of PK-PD targets have been described in critically ill patients [10,33,34,100–103]. However, the use of Bayesian dosing software to achieve these targets and its impact on clinical outcomes have yet to be evaluated but are still needed.

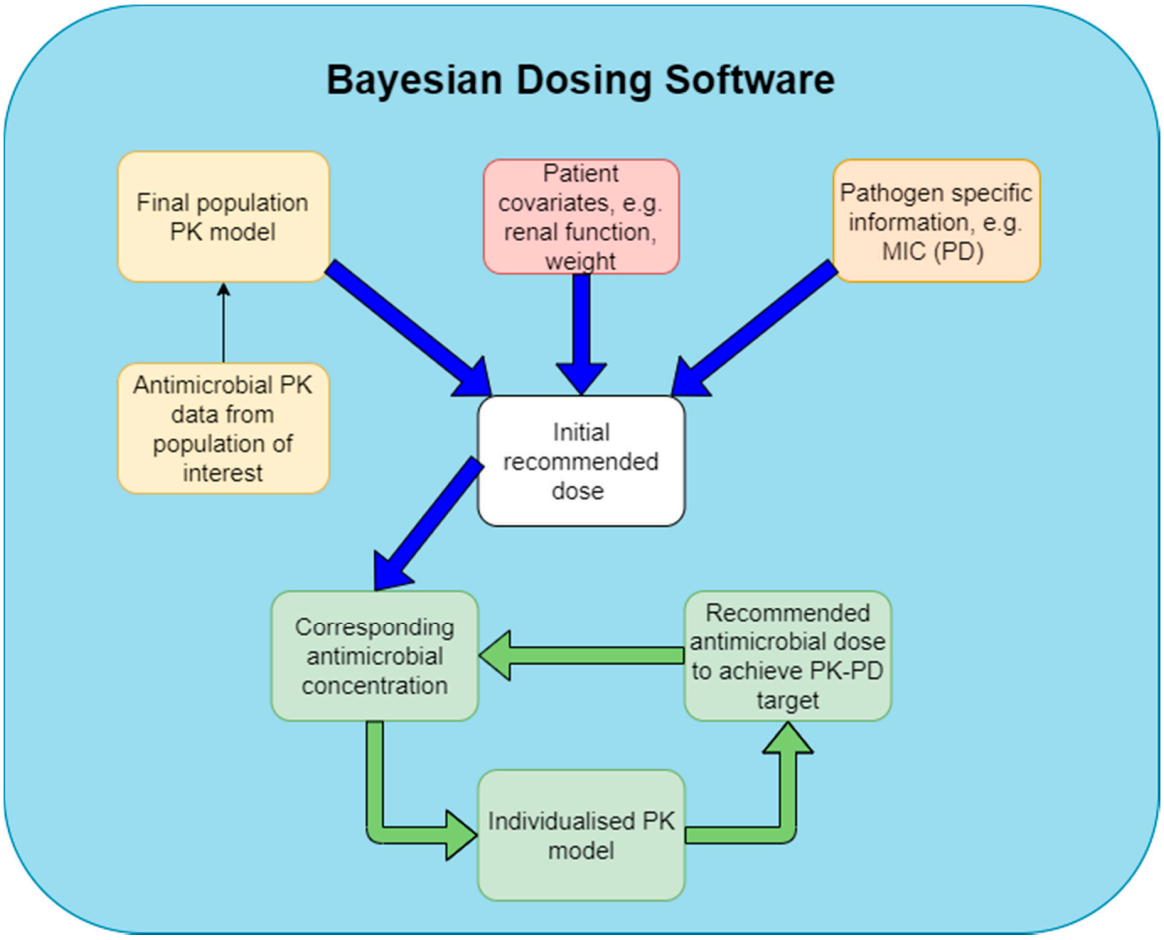

Figure 3. Bayesian forecasting based dosing software (blue) initially utilises patient covariates (red), PK properties of the antimicrobial (yellow), and pathogen PD properties (orange) to generate an initial recommended dose that is likely to achieve the PK-PD target associated with maximum efficacy. Resulting plasma exposure concentrations from this dose can then be used to produce a refined PK model that is individualised to a specific patient. A new optimised dose is then produced that is specific to the patient and can be further refined if needed with additional TDM data (green cycle).

4.4. Artificial Intelligence Software

A relatively new approach to optimising treatment of critically ill patients with sepsis in the ICU is with the use of computerised programs that utilise artificial intelligence (AI) in generating their recommendations. Unlike dosing software with Bayesian forecasting which uses PK and statistical modelling to individualise therapy to patients, AI software uses reinforcement learning to generate recommendations on appropriate interventions required to achieve predetermined targets for patients [104]. Artificial intelligence software examines data from large patient population databases to identify interventions associated with the target outcome and combines this information with an individual patient's characteristics to determine the most appropriate intervention that will maximise the probability of achieving the predefined outcome [105,106]. If the predetermined outcome is not achieved, clinicians are able to relay this information back to the AI software which will then further refine its algorithm to alter recommendations to help achieve the target (similar to a trial-and-error approach).

Although there is preliminary evidence that highlights the potential utility of AI software for optimising the treatment of patients in the ICU [107], evidence for AI software use for optimising the dosing of antimicrobials in the ICU is lacking. The dosing software InsightRx, which utilises both Bayesian forecasting and AI [108], has been observed to accurately predict the AUC of vancomycin

based on one trough concentration ($AUC_{InsightRx}$: $AUC_{reference}$ of 0.84 with 25th–75th median percentile of 0.77–0.88, accuracy was improved when two concentrations were used) [97]. In this study, InsightRx performed similarly well to other dosing software that utilise only Bayesian forecasting for predicting vancomycin AUC. InsightRx's ability to recommend dosing changes and its impact on achieving target AUC has not been evaluated in critically ill patients.

One potential benefit of AI-based dosing programs over other dosing software is the potential for AI software to consider the impact of interacting drugs on antimicrobial concentrations (such as that mediated by cytochrome enzyme induction or inhibition). If embedded within the electronic health records, AI programs may potentially identify medications through its databases where concurrent prescribing with an antimicrobial result in alterations to antimicrobial plasma concentrations [109,110]. The software could potentially make proactive dosing recommendations to compensate for such drug interactions and maximise the likelihood that antimicrobial PK-PD targets could be achieved. However, this has yet to be prospectively evaluated in critically ill patients.

4.5. Challenges ahead for Widespread Dosing Software

As described above, there are currently many types of dosing software that utilise different models when generating dosing recommendations. This may pose a barrier to clinicians as there is insufficient data to support superiority of one model over another. Although complex programs that utilise Bayesian forecasting and/or AI may produce dosing recommendations that are more likely to achieve PK-PD targets, this has yet to be adequately examined in the critically ill cohort. Studies powered to examine the comparative predictive accuracy of dosing recommendations of these programs are needed before clinicians are able to confidently adopt one program over another into their clinical workflows. Additionally, studies powered to quantify clinical outcomes such as sepsis-related mortality are needed before widespread use can be recommended.

Another potential barrier associated with using dosing software in the clinical setting is the adequate knowledge and training required by users [111]. This includes familiarisation with the software as well as ensuring that they have sufficient understanding of antimicrobial PK-PD. Clinicians would need to develop knowledge of concepts related to MICs and the interrelationship with antimicrobial PK-PD so that appropriate exposure targets are selected. This may be lacking unless clinicians are trained in the areas of microbiology or infectious diseases [112]. Potential solutions may include utilisation and integration of specialised clinical pharmacists or pharmacologists into the critical care team who are trained in using dosing software to assist with complex dosing [113]. Furthermore, not all ICUs have access to the different drug assays needed to generate TDM results for antimicrobials which are required by software to generate optimised dosing recommendations.

Currently, most dosing softwares are either web-based or standalone applications [5,108]. This potentially detracts from the usability of the dosing programs given clinicians will be required to manually extract data from hospital-based medical records, input data into the dosing program, generate the recommended doses and then return back to the medical records to amend the dose [108]. In health services where clinicians are often time-poor, this may pose a significant barrier to wide-spread adoption of this technology. Several dosing software programs have been developed to integrate with hospital-based medical records for non-antimicrobial drugs outside of the ICU and these programs have been deemed satisfactory as perceived by clinicians [114]. Pleasingly, some commercial program developers have highlighted the ability for their dosing software for antimicrobials to be integrated with local electronic health record platforms, thus potentially improving clinical workflows in the ICU.

If research shows that dosing software confers patient-centred outcome benefits, then before being able to be widely used clinically, several challenges must be addressed. Currently, few dosing software programs are registered as medical devices with national regulatory bodies. Although clinicians are still responsible for accepting the recommendations from the dosing software program, a reliance on this technology for dosing is likely to raise concerns regarding the accuracy and safety of these programs if they are unregulated beyond the internal quality control processes of the software developers [115].

In the future, software developers may be required to register their dosing software with relevant regulatory bodies before health services are able to incorporate this technology into their workforce.

Although favourable cost outcomes from using dosing software have been reported [116,117], this analysis has yet to be conducted in critically ill patients. Costs that healthcare networks need to consider include the resources needed to train clinicians to use the software, costs associated with integrating dosing software with local electronic health records as well as the physical infrastructure needed to house dosing software along with the large amount of data that is likely to be generated from performing dosing simulations. A potential cost-efficient option for these networks to consider when investing in dosing software is to select software capable of providing support across a wide range of clinical settings, as opposed to programs that only specialise in one or two clinical areas.

5. Conclusions

Dosing of antimicrobials in critically ill patients with sepsis remains a challenging area. Due to the changes in physiology typically seen in these patients, adopting dosing regimens from non-critical care patients are unlikely to achieve desired PK-PD targets that are associated with optimal outcomes. There are several approaches that can be employed by clinicians to increase the likelihood of achieving these antimicrobial targets in critically ill patients. Where available, clinicians should consider using dosing nomograms and/or TDM to support their dosing strategies to improve the likelihood of achieving PK-PD targets that are associated with positive clinical outcomes. Dosing nomograms are generally easy to integrate into clinical practice and do not require extensive resources beyond clinician training. TDM can help identify patients who have not achieved PK-PD targets or who may have developed toxic concentrations which are predisposed to adverse effects. Clinicians can then use TDM results to alter dosing regimens by a magnitude they anticipate will achieve PK-PD targets or in conjunction with other tools such as dosing nomograms or dosing software programs to improve the dosing accuracy of these tools.

Other dose optimisation strategies that may have increased precision for achieving antimicrobial PK-PD targets, of which dosing software is a promising tool. Other dose optimisation strategies exist, such as dosing software, which may offer recommendations that achieve PK-PD targets with increased precision. Simpler dosing programs that utilise linear regression or population-based models may be suitable and are easier to implement, especially in centres that have limited resources. In centres with access to clinicians trained to alter antimicrobial dosages to achieve PK-PD targets, dosing software with Bayesian forecasting and/or AI may provide additional precision to improve antimicrobial dosing.

Importantly, future studies describing the clinical outcomes and cost-benefits associated with using dosing software and AI are needed and it is hoped that this data will help consolidate the utilisation of this technology in patients that are high risk of dying from infections. In the meantime, clinicians should at least consider using dosing nomograms and/or TDM to support their dosing strategies to improve the likelihood of achieving PK-PD targets that are associated with positive clinical outcomes.

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Appendix A

Table A1. Antimicrobial population PK models developed from critical care patient groups.

Antimicrobial	Study Profile	Reference
Aminoglycosides	• Adult medical ICU. • N = 102 patients (211 plasma concentration samples). • Using gentamicin and tobramycin. • Exclusion—RRT, loading dose less than 3 mg/kg, cystic fibrosis patients and solid organ transplant patients. • Model covariate—glomerular filtration rate (simplified 4-variable Modified Diet in Renal Disease) and actual body weight.	Rea RS et al. [118]
Amoxicillin and clavulanic acid	• Adult ICU. • N = 13 patients (104 plasma samples). • Exclusion—RRT. • Model covariate—creatinine clearance (24-h urine collection).	Carlier M et al. [119]
Cefazolin	• Adult trauma ICU. • N = 30 patients (150 plasma samples). • Exclusion—RRT, renal impairment (plasma creatinine > 171 micromol/L). • Model covariates—creatinine clearance (method of calculation not reported), plasma albumin concentration, actual body weight.	Roberts JA et al. [120]
Cefepime	• Adult mixed surgical and medical ICU. • N = 26 patients (72 plasma samples). • Population with ventilator associated pneumonia • Exclusion—RRT. • Model covariates—creatinine clearance (Cockcroft-Gault), actual body weight.	Nicasio AM et al. [121]
Cefotaxime	• Paediatric ICU (range 0.2—229 months old). • N = 49 patients (Total samples reported as median of 2 per patient, range = 1–4). • Exclusion—kidney or liver transplant within last 2 weeks, ECMO, RRT. • Model covariates—actual body weight and post-natal age.	Beranger A et al. [122]
Ceftazidime	• Georges B et al. • Adult ICU. • N = 49 patients (443 plasma samples). • Population with *P. aeruginosa* infections sensitive to ceftazidime. • Exclusion—not reported. • Model covariates—creatinine clearance (Modified Diet in Renal Disease), presence of mechanical ventilation, reason for admission (medical vs. surgical patients).	Georges B et al. [123]
Ceftazidime (pediatric)	• Paediatric ICU (range 0.1–2.0 years old). • N = 51 patients (90 plasma concentrations). • Exclusion – preterm newborns (gestational age < 37 weeks) with survival times less than treatment cycle and other factors deemed unsuitable by researchers. • Model covariates—actual body weight, creatinine clearance (Schwartz).	Shi ZR et al. Shi, Chen [124]

Table A1. *Cont.*

Antimicrobial	Study Profile	Reference
Ceftolazone and tazobactam	• Adult ICU. • N = 12 patients (133 plasma samples). • Exclusion—RRT, received piperacillin-tazobactam in preceding 7 days, pregnant. • Model covariate—creatinine clearance (24-h urinary creatinine clearance).	Sime FB et al. [125]
Ceftriaxone	• Garot D et al. • Adult ICU. • N = 54 patients (12 received RRT) (709 plasma concentrations). • Exclusion—chronic dialysis, life expectancy < 7 days, treatment with ceftriaxone for more than 24 h. • Model covariate—Creatinine clearance 24-h urine collection). • RRT was determined to not be a covariate. • Leegwater E et al. • Adult ICU. • N = 55 patients (110 plasma samples). • Exclusion—RRT, life expectancy < 12 h. • Model covariates—adjusted body weight, plasma albumin concentration, creatinine clearance (Cockcroft-Gault), method of administration (continuous infusion or intermittent bolus).	Garot D et al. [126] Leegwater E et al. [127] [126,127]
Ciprofloxacin	• Adult ICU. • N = 102 patients (588 plasma samples). • Exclusion—not reported. • Model covariate—creatinine clearance (Cockcroft-Gault).	Khachman D et al. [128]
Doripenem	• Adult ICU. • N = 12 patients (140 plasma samples). • Exclusion—RRT, pregnant or lactating. • Model covariate—creatinine clearance (Cockcroft-Gault).	Abdul-Aziz MH et al. [129]
Flucloxacillin	• Adult ICU. • N = 10 patients (67 plasma concentrations and 10 urine concentrations). • Exclusion—not reported. • Model covariates—body mass index, creatinine clearance (4 or 6-h urine collection).	Ulldemolins M et al. [130]
Fluconazole	• Adult ICU. • N = 76 patients (295 plasma samples). • Exclusion—not reported. • Model covariates—Creatinine clearance (Cockroft-Gault), actual body weight.	Aoyama T et al. [131]
Fosfomycin	• Adult ICU. • N = 12 patients (515 plasma samples). • Exclusion—Fosfomycin use in previous month, pregnancy or lactation. • Model covariates—creatinine clearance (Cockroft-Gault), actual body weight.	Parker SL et al. [132]
Ganciclovir	• Adult ICU. • N = 34 patients (128 plasma samples). • Exclusion—Ganciclovir therapy following discharge from ICU for > 24 h. • Model covariates—estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration).	Kren SD et al. [133]

Table A1. *Cont.*

Antimicrobial	Study Profile	Reference
Imipenem	• Adult ICU. • N = 26 patients (138 samples). • Exclusion—creatinine clearance < 60 mL/min (Cockroft-Gault), BMI < 18 or >30, pregnancy. • Model covariate—estimated glomerular filtration rate unadjusted for body surface area (Chronic Kidney Disease Epidemiology Collaboration).	De Velde F [134]
Levofloxacin	• Adult ICU and non-critically ill patients. • N = 18 ICU patients and 17 non-critically ill patients (total of 329 samples). • Exclusion—RRT. • Model covariate—creatinine clearance (Cockroft-Gault). • There was no impact from critical illness on final model.	Roberts JA et al. [135]
Linezolid	• Adult ICU. • N = 40 patients (311 plasma samples). • Exclusion—Pregnancy, use of medications that inhibit monoamine oxidase A or B. • Model covariates—creatinine clearance (24-h urine collection), ECMO, RRT effluent flow rate.	Soraluce A et al. [136]
Meropenem	• Crandon JL. • Mixed surgical and medical adult ICU. • N = 26 patients (67 plasma samples). • Exclusion—RRT. • Model covariates—creatinine clearance (Cockroft-Gault), adjusted body weight Braune S. • Adult ICU. • N = 19 patients (308 plasma samples). • Population using meropenem in patients receiving RRT (sustained low-efficiency dialysis). • Exclusion—not reported. • Model covariates—Presence of RRT (on or off), amount of residual diuresis. • Rapp M et al. • Paediatric ICU (Range 1.4—187.2 months). • N = 40 patients (121 plasma samples). • Exclusion—kidney or liver transplant in prior 2 weeks. • Model covariates—RRT, actual body weight, estimated glomerular filtration rate (Schwartz).	Crandon Jl et al. [137] Braune S et al. [138] Rapp M et al. [139]
Micafungin	• Adult ICU. • N = 11 patients (242 plasma samples). • Population using micafungin in obese and morbidly obese patients. • Exclusion—not reported. • Model covariates—body weight (normalised to 70 kg), age (normalised to 60 years).	Maseda E et al. [140]
Piperacillin and tazobactam	• Adult ICU. • N = 146 patients (803 plasma samples). • Exclusion—not reported. • Model covariates—creatinine clearance (Cockroft-Gault), actual body weight.	Felton TW et al. [141]
Polymyxin B	• Adult ICU. • N = 24 patients (192 plasma samples). • Exclusion—not reported. • Model covariate—actual body weight. • RRT was determined to not be a covariate (samples from 2 patients only).	Sandri AM et al. [142]

Table A1. *Cont.*

Antimicrobial	Study Profile	Reference
Posaconazole	• Adult ICU. • N = 8 patients (112 plasma samples). • Exclusion—pregnancy, drugs interacting with posaconazole, use of posaconazole in preceding 2 weeks. • Model covariates—plasma albumin concentration and body mass index.	Sime FB et al. [143]
Tigecycline	• Adult ICU. • N = 10 patients (90 plasma samples). • Exclusion—not reported. • Model covariate—body mass index.	Xie J et al. [144]
Vancomycin	• Adult ICU. • N = 47 patients (569 plasma samples). • Exclusion—not reported. • Model covariate—creatinine clearance (Cockroft-Gault).	Neely MN et al. [90]

References

1. Ferrer, R.; Martin-Loeches, I.; Phillips, G.; Osborn, T.M.; Townsend, S.; Dellinger, R.P.; Artigas, A.; Schorr, C.; Levy, M.M. Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program. *Crit. Care Med.* **2014**, *42*, 1749–1755. [CrossRef] [PubMed]
2. Kumar, A.; Ellis, P.; Arabi, Y.; Roberts, D.; Light, B.; Parrillo, J.E.; Dodek, P.; Wood, G.; Kumar, A.; Simon, D.; et al. Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock. *Chest* **2009**, *136*, 1237–1248. [CrossRef] [PubMed]
3. Kumar, A.; Roberts, D.; Wood, K.E.; Light, B.; Parrillo, J.E.; Sharma, S.; Suppes, R.; Feinstein, D.; Zanotti, S.; Taiberg, L.; et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit. Care Med.* **2006**, *34*, 1589–1596. [CrossRef] [PubMed]
4. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med.* **2017**, *45*, 486–552. [CrossRef]
5. Roberts, J.A.; Abdul-Aziz, M.H.; Lipman, J.; Mouton, J.W.; Vinks, A.A.; Felton, T.W.; Hope, W.W.; Farkas, A.; Neely, M.N.; Schentag, J.J.; et al. Individualised antibiotic dosing for patients who are critically ill: Challenges and potential solutions. *Lancet Infect. Dis.* **2014**, *14*, 498–509. [CrossRef]
6. Bhattaram, V.A.; Bonapace, C.; Chilukuri, D.M.; Duan, J.Z.; Garnett, C.; Gobburu, J.V.S.; Jang, S.H.; Kenna, L.; Lesko, L.J.; Madabushi, R.; et al. Impact of Pharmacometric Reviews on New Drug Approval and Labeling Decisions—A Survey of 31 New Drug Applications Submitted Between 2005 and 2006. *Clin. Pharmacol. Ther.* **2007**, *81*, 213–221. [CrossRef]
7. Tuntland, T.; Ethell, B.; Kosaka, T.; Blasco, F.; Zang, R.X.; Jain, M.; Gould, T.; Hoffmaster, K. Implementation of pharmacokinetic and pharmacodynamic strategies in early research phases of drug discovery and development at Novartis Institute of Biomedical Research. *Front. Pharmacol.* **2014**, *5*, 174. [CrossRef]
8. Roberts, J.A. Using PK/PD to optimize antibiotic dosing for critically ill patients. *Curr. Pharm. Biotechnol.* **2011**, *12*, 2070–2079. [CrossRef]
9. Sime, F.B.; Roberts, M.S.; Peake, S.L.; Lipman, J.; Roberts, J.A. Does Beta-lactam Pharmacokinetic Variability in Critically Ill Patients Justify Therapeutic Drug Monitoring? A Systematic Review. *Ann. Intensive Care.* **2012**, *2*, 35. [CrossRef] [PubMed]
10. Roberts, J.A.; Paul, S.K.; Akova, M.; Bassetti, M.; De Waele, J.J.; Dimopoulos, G.; Kaukonen, K.M.; Koulenti, D.; Martin, C.; Montravers, P.; et al. DALI: Defining antibiotic levels in intensive care unit patients: Are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis.* **2014**, *58*, 1072–1083. [CrossRef]

11. Sinnollareddy, M.G.; Roberts, M.S.; Lipman, J.; Roberts, J.A. β-Lactam pharmacokinetics and pharmacodynamics in critically ill patients and strategies for dose optimization: A structured review. *Clin. Exp. Pharmacol. Physiol.* **2012**, *39*, 489–496. [CrossRef] [PubMed]
12. Aspasia Soulatati, S.P.D. Liver dysfunction in the intensive care unit. *Ann. Gastroenterol.* **2005**, *18*, 35–45.
13. Kramer, L.; Jordan, B.; Druml, W.; Bauer, P.; Metnitz, P.G. Incidence and prognosis of early hepatic dysfunction in critically ill patients—A prospective multicenter study. *Crit Care Med.* **2007**, *35*, 1099–1104. [CrossRef]
14. Saloojee, A.; Skinner, D.L.; Loots, E.; Hardcastle, T.C.; Muckart, D.J.J. Hepatic dysfunction: A common occurrence in severely injured patients. *Injury* **2017**, *48*, 127–132. [CrossRef] [PubMed]
15. Bouchard, J.; Acharya, A.; Cerda, J.; Maccariello, E.R.; Madarasu, R.C.; Tolwani, A.J.; Liang, X.; Fu, P.; Liu, Z.H.; Mehta, R.L. A Prospective International Multicenter Study of AKI in the Intensive Care Unit. *Clin. J. Am. Soc. Nephrol. CJASN* **2015**, *10*, 1324–1331. [CrossRef]
16. Hoste, E.A.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef]
17. Mehta, R.L.; Pascual, M.T.; Soroko, S.; Savage, B.R.; Himmelfarb, J.; Ikizler, T.A.; Paganini, E.P.; Chertow, G.M. Spectrum of acute renal failure in the intensive care unit: The PICARD experience. *Kidney Int.* **2004**, *66*, 1613–1621. [CrossRef] [PubMed]
18. Uchino, S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *Jama* **2005**, *294*, 813–818. [CrossRef] [PubMed]
19. Blot, S.I.; Pea, F.; Lipman, J. The effect of pathophysiology on pharmacokinetics in the critically ill patient—Concepts appraised by the example of antimicrobial agents. *Adv. Drug Deliv. Rev.* **2014**, *77*, 3–11. [CrossRef]
20. Halilovic, J.; Heintz, B.H. Antibiotic dosing in cirrhosis. *Am. J. Health Syst. Pharm. AJHP Off. J. Am. Soc. Health Syst. Pharm.* **2014**, *71*, 1621–1634. [CrossRef] [PubMed]
21. Bilbao-Meseguer, I.; Rodríguez-Gascón, A.; Barrasa, H.; Isla, A.; Solinís, M. Augmented Renal Clearance in Critically Ill Patients: A Systematic Review. *Clin. Pharmacokinet.* **2018**, *57*, 1107–1121. [CrossRef] [PubMed]
22. Udy, A.A.; Putt, M.T.; Shanmugathasan, S.; Roberts, J.A.; Lipman, J. Augmented renal clearance in the Intensive Care Unit: An illustrative case series. *Int. J. Antimicrob. Agents* **2010**, *35*, 606–608. [CrossRef] [PubMed]
23. Sime, F.B.; Udy, A.A.; Roberts, J.A. Augmented renal clearance in critically ill patients: Etiology, definition and implications for beta-lactam dose optimization. *Curr. Opin. Pharmacol.* **2015**, *24*, 1–6. [CrossRef] [PubMed]
24. Ulldemolins, M.; Roberts, J.A.; Rello, J.; Paterson, D.L.; Lipman, J. The Effects of Hypoalbuminaemia on Optimizing Antibacterial Dosing in Critically Ill Patients. *Clin. Pharmacokinet.* **2011**, *50*, 99–110. [CrossRef] [PubMed]
25. Varghese, J.M.; Roberts, J.A.; Lipman, J. Pharmacokinetics and pharmacodynamics in critically ill patients. *Curr. Opin. Anaesthesiol.* **2010**, *23*, 472–478. [CrossRef] [PubMed]
26. Tsai, D.; Lipman, J.; Roberts, J.A. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. *Curr. Opin. Crit. Care* **2015**, *21*, 412–420. [CrossRef]
27. Boucher, B.A.; Wood, G.C.; Swanson, J.M. Pharmacokinetic changes in critical illness. *Crit. Care Clin.* **2006**, *22*, 255–271. [CrossRef]
28. Smith, B.S.; Yogaratnam, D.; Levasseur-Franklin, K.E.; Forni, A.; Fong, J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest* **2012**, *141*, 1327–1336. [CrossRef]
29. Abdul-Aziz, M.H.; Roberts, J.A. Antibiotic dosing during extracorporeal membrane oxygenation: Does the system matter? *Curr. Opin. Anaesthesiol.* **2020**, *33*, 71–82. [CrossRef]
30. Zamoner, W.; de Freitas, F.M.; Garms, D.S.S.; de Oliveira, M.G.; Balbi, A.L.; Ponce, D. Pharmacokinetics and pharmacodynamics of antibiotics in critically ill acute kidney injury patients. *Pharmacol. Res. Perspect.* **2016**, *4*, e00280. [CrossRef]
31. Cheng, V.; Abdul-Aziz, M.-H.; Roberts, J.A.; Shekar, K. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. *J. Thorac Dis.* **2018**, *10* (Suppl. 5), S629–S641. [CrossRef] [PubMed]
32. Fissell, W.H. Antimicrobial dosing in acute renal replacement. *Adv. Chronic Kidney Dis.* **2013**, *20*, 85–93. [CrossRef]

33. Forrest, A.; Nix, D.E.; Ballow, C.H.; Goss, T.F.; Birmingham, M.C.; Schentag, J.J. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob. Agents Chemother.* **1993**, *37*, 1073–1081. [CrossRef] [PubMed]
34. McKinnon, P.S.; Paladino, J.A.; Schentag, J.J. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int. J. Antimicrob. Agents* **2008**, *31*, 345–351. [CrossRef]
35. Carrie, C.; Petit, L.; d'Houdain, N.; Sauvage, N.; Cottenceau, V.; Lafitte, M.; Foumenteze, C.; Hisz, Q.; Menu, D.; Legeron, R.; et al. Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of beta-lactams administered by continuous infusion: A prospective observational study. *Int. J. Antimicrob. Agents* **2018**, *51*, 443–449. [CrossRef]
36. Moise-Broder, P.A.; Forrest, A.; Birmingham, M.C.; Schentag, J.J. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. *Clin. Pharmacokinet.* **2004**, *43*, 925–942. [CrossRef]
37. Li, C.; Du, X.; Kuti, J.L.; Nicolau, D.P. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. *Antimicrob. Agents Chemother.* **2007**, *51*, 1725–1730. [CrossRef]
38. Mouton, J.W.; Muller, A.E.; Canton, R.; Giske, C.G.; Kahlmeter, G.; Turnidge, J. MIC-based dose adjustment: Facts and fables. *J. Antimicrob. Chemother.* **2018**, *73*, 564–568. [CrossRef]
39. Roberts, J.A.; Lipman, J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit. Care Med.* **2009**, *37*, 840–851. [CrossRef] [PubMed]
40. Rea, R.S.; Capitano, B. Optimizing use of aminoglycosides in the critically ill. *Semin Respir. Crit. Care Med.* **2007**, *28*, 596–603. [CrossRef] [PubMed]
41. Muller, A.E.; Huttner, B.; Huttner, A. Therapeutic Drug Monitoring of Beta-Lactams and Other Antibiotics in the Intensive Care Unit: Which Agents, Which Patients and Which Infections? *Drugs* **2018**, *78*, 439–451. [CrossRef] [PubMed]
42. Zelenitsky, S.A.; Ariano, R.E. Support for higher ciprofloxacin AUC 24/MIC targets in treating Enterobacteriaceae bloodstream infection. *J. Antimicrob. Chemother.* **2010**, *65*, 1725–1732. [CrossRef]
43. Rybak, M.; Lomaestro, B.; Rotschafer, J.C.; Moellering, R., Jr.; Craig, W.; Billeter, M.; Dalovisio, J.R.; Levine, D.P. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am. J. Health Syst. Pharmacy* **2009**, *66*, 82–98. [CrossRef] [PubMed]
44. Meagher, A.K.; Passarell, J.A.; Cirincione, B.B.; Van Wart, S.A.; Liolios, K.; Babinchak, T.; Ellis-Grosse, E.J.; Ambrose, P.G. Exposure-response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. *Antimicrob. Agents Chemother.* **2007**, *51*, 1939–1945. [CrossRef] [PubMed]
45. Passarell, J.A.; Meagher, A.K.; Liolios, K.; Cirincione, B.B.; Van Wart, S.A.; Babinchak, T.; Ellis-Grosse, E.J.; Ambrose, P.G. Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. *Antimicrob. Agents Chemother.* **2008**, *52*, 204–210. [CrossRef] [PubMed]
46. Craig, W.A. Does the dose matter? *Clin Infect Dis.* **2001**, *33* (Suppl. 3), S233–S237. [CrossRef]
47. Louie, A.; Kaw, P.; Liu, W.; Jumbe, N.; Miller, M.H.; Drusano, G.L. Pharmacodynamics of daptomycin in a murine thigh model of Staphylococcus aureus infection. *Antimicrob. Agents Chemother.* **2001**, *45*, 845–851. [CrossRef]
48. Girard, D.; Finegan, S.M.; Dunne, M.W.; Lame, M.E. Enhanced efficacy of single-dose versus multi-dose azithromycin regimens in preclinical infection models. *J. Antimicrob. Chemother.* **2005**, *56*, 365–371. [CrossRef]
49. Vogelman, B.; Gudmundsson, S.; Leggett, J.; Turnidge, J.; Ebert, S.; Craig, W.A. Correlation of Antimicrobial Pharmacokinetic Parameters with Therapeutic Efficacy in an Animal Model. *J. Infect. Dis.* **1988**, *158*, 831–847. [CrossRef]
50. Pea, F.; Viale, P.; Cojutti, P.; Del Pin, B.; Zamparini, E.; Furlanut, M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. *J. Antimicrob. Chemother.* **2012**, *67*, 2034–2042. [CrossRef]
51. Bergen, P.J.; Li, J.; Nation, R.L. Dosing of colistin-back to basic PK/PD. *Curr. Opin. Pharmacol.* **2011**, *11*, 464–469. [CrossRef] [PubMed]
52. Lepak, A.J.; Andes, D.R. Antifungal pharmacokinetics and pharmacodynamics. *Cold Spring Harb. Perspect. Med.* **2014**, *5*, a019653. [CrossRef]

53. Perez-Pitarch, A.; Ferriols-Lisart, R.; Aguilar, G.; Ezquer-Garin, C.; Belda, F.J.; Guglieri-Lopez, B. Dosing of caspofungin based on a pharmacokinetic/pharmacodynamic index for the treatment of invasive fungal infections in critically ill patients on continuous venovenous haemodiafiltration. *Int. J. Antimicrob. Agents* **2018**, *51*, 115–121. [CrossRef]
54. Hong, Y.; Shaw, P.J.; Nath, C.E.; Yadav, S.P.; Stephen, K.R.; Earl, J.W.; McLachlan, A.J. Population pharmacokinetics of liposomal amphotericin B in pediatric patients with malignant diseases. *Antimicrob. Agents Chemother.* **2006**, *50*, 935–942. [CrossRef]
55. Leblebicioglu, H.; Cakir, N.; Celen, M.; Kurt, H.; Baris, H.; Laeuffer, J. Comparative activity of carbapenem testing (the COMPACT study) in Turkey. *BMC Infect Dis.* **2012**, *12*, 42. [CrossRef] [PubMed]
56. Kiratisin, P.; Chongthaleong, A.; Tan, T.Y.; Lagamayo, E.; Roberts, S.; Garcia, J.; Davies, T. Comparative in vitro activity of carbapenems against major Gram-negative pathogens: Results of Asia-Pacific surveillance from the COMPACT II study. *Int. J. Antimicrob. Agents* **2012**, *39*, 311–316. [CrossRef] [PubMed]
57. Valenza, G.; Seifert, H.; Decker-Burgard, S.; Laeuffer, J.; Morrissey, I.; Mutters, R. Comparative Activity of Carbapenem Testing (COMPACT) study in Germany. *Int. J. Antimicrob. Agents* **2012**, *39*, 255–258. [CrossRef]
58. Hidron, A.I.; Edwards, J.R.; Patel, J.; Horan, T.C.; Sievert, D.M.; Pollock, D.A.; Fridkin, S.K. NHSN annual update: Antimicrobial-resistant pathogens associated with healthcare-associated infections: Annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect. Control Hosp. Epidemiol.* **2008**, *29*, 996–1011. [CrossRef]
59. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992–April 2000, issued June 2000. *Am. J. Infect. Control* **2000**, *28*, 429–448. [CrossRef]
60. Vincent, J.L.; Bihari, D.J.; Suter, P.M.; Bruining, H.A.; White, J.; Nicolas-Chanoin, M.H.; Wolff, M.; Spencer, R.C.; Hemmer, M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *Jama* **1995**, *274*, 639–644. [CrossRef]
61. Hanberger, H.; Garcia-Rodriguez, J.A.; Gobernado, M.; Goossens, H.; Nilsson, L.E.; Struelens, M.J. Antibiotic susceptibility among aerobic gram-negative bacilli in intensive care units in 5 European countries. French and Portuguese ICU Study Groups. *Jama* **1999**, *281*, 67–71. [CrossRef] [PubMed]
62. Levison, M.E.; Levison, J.H. Pharmacokinetics and pharmacodynamics of antibacterial agents. *Infect. Dis. Clin. North Am.* **2009**, *23*, 791–815. [CrossRef]
63. Roberts, J.A.; Kruger, P.; Paterson, D.L.; Lipman, J. Antibiotic resistance—What's dosing got to do with it? *Crit Care Med.* **2008**, *36*, 2433–2440. [CrossRef]
64. Chennavasin, P.; Brater, D.C. Nomograms for Drug Use in Renal Disease. *Clin. Pharmacokinet.* **1981**, *6*, 193–214. [CrossRef] [PubMed]
65. Burton, M.E. *Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring*, 4th ed.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2006.
66. Lewis, S.J.; Mueller, B.A. Development of a vancomycin dosing approach for critically ill patients receiving hybrid hemodialysis using Monte Carlo simulation. *SAGE Open Med.* **2018**, *6*, 2050312118773257. [CrossRef] [PubMed]
67. Baptista, J.P.; Roberts, J.A.; Sousa, E.; Freitas, R.; Deveza, N.; Pimentel, J. Decreasing the time to achieve therapeutic vancomycin concentrations in critically ill patients: Developing and testing of a dosing nomogram. *Crit. Care* **2014**, *18*, 654. [CrossRef]
68. Medellin-Garibay, S.E.; Romano-Moreno, S.; Tejedor-Prado, P.; Rubio-Alvaro, N.; Rueda-Naharro, A.; Blasco-Navalpotro, M.A.; Garcia, B.; Barcia, E. Influence of Mechanical Ventilation on the Pharmacokinetics of Vancomycin Administered by Continuous Infusion in Critically Ill Patients. *Antimicrob. Agents Chemother.* **2017**, *61*. [CrossRef]
69. Pea, F.; Furlanut, M.; Negri, C.; Pavan, F.; Crapis, M.; Cristini, F.; Viale, P. Prospectively validated dosing nomograms for maximizing the pharmacodynamics of vancomycin administered by continuous infusion in critically ill patients. *Antimicrob. Agents Chemother.* **2009**, *53*, 1863–1867. [CrossRef]
70. Crumby, T.; Rinehart, E.; Carby, M.C.; Kuhl, D.; Talati, A.J. Pharmacokinetic comparison of nomogram-based and individualized vancomycin regimens in neonates. *Am. J. Health Syst. Pharm. AJHP. Off. J. Am. Soc. Health Syst. Pharm.* **2009**, *66*, 149–153. [CrossRef]

71. Miloslavsky, M.; Galler, M.F.; Moawad, I.; Actis, J.; Cummings, B.M.; El Saleeby, C.M. The Impact of Pediatric-Specific Vancomycin Dosing Guidelines: A Quality Improvement Initiative. *Pediatrics* **2017**, *139*, e20162423. [CrossRef] [PubMed]
72. Watling, S.M.; Kisor, D.F. Population pharmacokinetics: Development of a medical intensive care unit-specific gentamicin dosing nomogram. *Ann. Pharmacother.* **1993**, *27*, 151–154. [CrossRef] [PubMed]
73. Pea, F.; Viale, P.; Cojutti, P.; Furlanut, M. Dosing Nomograms for Attaining Optimum Concentrations of Meropenem by Continuous Infusion in Critically Ill Patients with Severe Gram-Negative Infections: A Pharmacokinetics/Pharmacodynamics-Based Approach. *Antimicrob. Agents Chemother.* **2012**, *56*, 6343. [CrossRef]
74. Minichmayr, I.K.; Roberts, J.A.; Frey, O.R.; Roehr, A.C.; Kloft, C.; Brinkmann, A. Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model. *J. Antimicrob. Chemoth.* **2018**, *73*, 1330–1339. [CrossRef] [PubMed]
75. Reeves, D.; Lovering, A.; Thomson, A. Therapeutic drug monitoring in the past 40 years of the Journal of Antimicrobial Chemotherapy. *J. Antimicrob. Chemother.* **2016**, *71*, 3330–3332. [CrossRef] [PubMed]
76. Prins, J.M.; Weverling, G.J.; de Blok, K.; van Ketel, R.J.; Speelman, P. Validation and nephrotoxicity of a simplified once-daily aminoglycoside dosing schedule and guidelines for monitoring therapy. *Antimicrob. Agents Chemother.* **1996**, *40*, 2494–2499. [CrossRef] [PubMed]
77. De Waele, J.J.; Carrette, S.; Carlier, M.; Stove, V.; Boelens, J.; Claeys, G.; Leroux-Roels, I.; Hoste, E.; Depuydt, P.; Decruyenaere, J.; et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: A randomised controlled trial. *Intensive Care Med.* **2014**, *40*, 380–987. [CrossRef]
78. Kadambari, S.; Heath, P.T.; Sharland, M.; Lewis, S.; Nichols, A.; Turner, M.A. Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units. *J. Antimicrob. Chemother.* **2011**, *66*, 2647–2650. [CrossRef]
79. Wong, G.; Brinkman, A.; Benefield, R.J.; Carlier, M.; De Waele, J.J.; El Helali, N.; Frey, O.; Harbarth, S.; Huttner, A.; McWhinney, B.; et al. An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J. Antimicrob. Chemother.* **2014**, *69*, 1416–1423. [CrossRef]
80. Tabah, A.; De Waele, J.; Lipman, J.; Zahar, J.R.; Cotta, M.O.; Barton, G.; Timsit, J.F.; Roberts, J.A. The ADMIN-ICU survey: A survey on antimicrobial dosing and monitoring in ICUs. *J. Antimicrob. Chemother.* **2015**, *70*, 2671–2677. [CrossRef]
81. Wong, G.; Sime, F.B.; Lipman, J.; Roberts, J.A. How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? *BMC Infect. Dis.* **2014**, *14*, 288. [CrossRef]
82. Mouton, J.W.; Theuretzbacher, U.; Craig, W.A.; Tulkens, P.M.; Derendorf, H.; Cars, O. Tissue concentrations: Do we ever learn? *J. Antimicrob. Chemother.* **2007**, *61*, 235–237. [CrossRef] [PubMed]
83. Kiem, S.; Schentag, J.J. Interpretation of Antibiotic Concentration Ratios Measured in Epithelial Lining Fluid. *Antimicrob. Agents Chemother.* **2008**, *52*, 24–36. [CrossRef]
84. Aulin, L.B.S.; Valitalo, P.A.; Rizk, M.L.; Visser, S.A.G.; Rao, G.; van der Graaf, P.H.; van Hasselt, J.G.C. Validation of a Model Predicting Anti-infective Lung Penetration in the Epithelial Lining Fluid of Humans. *Pharm. Res.* **2018**, *35*, 26. [CrossRef] [PubMed]
85. Jager, N.G.L.; van Hest, R.M.; Lipman, J.; Roberts, J.A.; Cotta, M.O. Antibiotic exposure at the site of infection: Principles and assessment of tissue penetration. *Expert Rev. Clin. Pharmacol.* **2019**, *12*, 623–634. [CrossRef] [PubMed]
86. Nau, R.; Sorgel, F.; Eiffert, H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin. Microbiol. Rev.* **2010**, *23*, 858–883. [CrossRef] [PubMed]
87. Musteata, F.M. Clinical Utility of Free Drug Monitoring. *Ther. Drug Monit. Newer Drugs Biomarkers* **2012**, 75–101. [CrossRef]
88. Briscoe, S.E.; McWhinney, B.C.; Lipman, J.; Roberts, J.A.; Ungerer, J.P. A method for determining the free (unbound) concentration of ten beta-lactam antibiotics in human plasma using high performance liquid chromatography with ultraviolet detection. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2012**, *907*, 178–184. [CrossRef]
89. Wong, G.; Briscoe, S.; Adnan, S.; McWhinney, B.; Ungerer, J.; Lipman, J.; Roberts, J.A. Protein binding of beta-lactam antibiotics in critically ill patients: Can we successfully predict unbound concentrations? *Antimicrob. Agents Chemother.* **2013**, *57*, 6165–6170. [CrossRef]

90. Neely, M.N.; Youn, G.; Jones, B.; Jelliffe, R.W.; Drusano, G.L.; Rodvold, K.A.; Lodise, T.P. Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrob. Agents Chemother.* **2014**, *58*, 309–316. [CrossRef]
91. Turnidge, J. Pharmacodynamics and dosing of aminoglycosides. *Infect. Dis. Clin. North Am.* **2003**, *17*, 503–528. [CrossRef]
92. Paterson, D.L.; Robson, J.M.; Wagener, M.M.; Peters, M. Monitoring of serum aminoglycoside levels with once-daily dosing. *Pathology* **1998**, *30*, 289–294. [CrossRef]
93. Mohan, M.; Batty, K.T.; Cooper, J.A.; Wojnar-Horton, R.E.; Ilett, K.F. Comparison of gentamicin dose estimates derived from manual calculations, the Australian 'Therapeutic Guidelines: Antibiotic' nomogram and the SeBA-GEN and DoseCalc software programs. *Br. J. Clin. Pharmacol.* **2004**, *58*, 521–527. [CrossRef] [PubMed]
94. Donagher, J.; Martin, J.H.; Barras, M.A. Individualised medicine: Why we need Bayesian dosing. *Int. Med. J.* **2017**, *47*, 593–600. [CrossRef] [PubMed]
95. Avent, M.L.; Rogers, B.A. Optimising antimicrobial therapy through the use of Bayesian dosing programs. *Int. J. Clin. Pharmacy* **2019**, *41*, 1121–1130. [CrossRef] [PubMed]
96. Sheiner, L.B.; Beal, S.; Rosenberg, B.; Marathe, V.V. Forecasting individual pharmacokinetics. *Clin. Pharmacol. Therapeut.* **1979**, *26*, 294–305. [CrossRef] [PubMed]
97. Turner, R.B.; Kojiro, K.; Shephard, E.A.; Won, R.; Chang, E.; Chan, D.; Elbarbry, F. Review and Validation of Bayesian Dose-Optimizing Software and Equations for Calculation of the Vancomycin Area Under the Curve in Critically Ill Patients. *Pharmacotherapy* **2018**, *38*, 1174–1183. [CrossRef]
98. Sheiner, L.B.; Beal, S.L. Bayesian individualization of pharmacokinetics: Simple implementation and comparison with non-Bayesian methods. *J. Pharm. Sci.* **1982**, *71*, 1344–1348. [CrossRef]
99. Heil, E.L.; Nicolau, D.P.; Farkas, A.; Roberts, J.A.; Thom, K.A. Pharmacodynamic Target Attainment for Cefepime, Meropenem, and Piperacillin-Tazobactam Using a Pharmacokinetic/Pharmacodynamic-Based Dosing Calculator in Critically Ill Patients. *Antimicrob. Agents Chemother.* **2018**, *62*, e01008-18. [CrossRef]
100. Crandon, J.L.; Bulik, C.C.; Kuti, J.L.; Nicolau, D.P. Clinical pharmacodynamics of cefepime in patients infected with Pseudomonas aeruginosa. *Antimicrob. Agents Chemother.* **2010**, *54*, 1111–1116. [CrossRef]
101. Muller, A.E.; Punt, N.; Mouton, J.W. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. *J. Antimicrob. Chemother.* **2013**, *68*, 900–906. [CrossRef]
102. MacVane, S.H.; Kuti, J.L.; Nicolau, D.P. Clinical pharmacodynamics of antipseudomonal cephalosporins in patients with ventilator-associated pneumonia. *Antimicrob. Agents Chemother.* **2014**, *58*, 1359–1364. [CrossRef] [PubMed]
103. Rhodes, N.J.; Kuti, J.L.; Nicolau, D.P.; Van Wart, S.; Nicasio, A.M.; Liu, J.; Lee, B.J.; Neely, M.N.; Scheetz, M.H. Defining Clinical Exposures of Cefepime for Gram-Negative Bloodstream Infections That Are Associated with Improved Survival. *Antimicrob. Agents Chemother.* **2015**, *60*, 1401–1410. [CrossRef] [PubMed]
104. Gottesman, O.; Johansson, F.; Komorowski, M.; Faisal, A.; Sontag, D.; Doshi-Velez, F.; Celi, L.A. Guidelines for reinforcement learning in healthcare. *Nat. Med.* **2019**, *25*, 16–18. [CrossRef] [PubMed]
105. Bennett, C.C.; Hauser, K. Artificial intelligence framework for simulating clinical decision-making: A Markov decision process approach. *Artif. Intell. Med.* **2013**, *57*, 9–19. [CrossRef]
106. Sutton, R.S.; Barto, A.G. *Reinforcement Learning: An Introduction*, 2nd ed.; MIT Press: Cambridge, MA, USA, 2018; pp. 1–526.
107. Komorowski, M.; Celi, L.A.; Badawi, O.; Gordon, A.C.; Faisal, A.A. The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. *Nat. Med.* **2018**, *24*, 1716–1720. [CrossRef]
108. Kantasiripitak, W.; Van Daele, R.; Gijsen, M.; Ferrante, M.; Spriet, I.; Dreesen, E. Software Tools for Model-Informed Precision Dosing: How Well Do They Satisfy the Needs? *Front. Pharmacol.* **2020**, *11*, 620. [CrossRef]
109. Ryu, J.Y.; Kim, H.U.; Lee, S.Y. Deep learning improves prediction of drug-drug and drug-food interactions. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E4304–E4311. [CrossRef] [PubMed]
110. Polasek, T.M.; Kirkpatrick, C.M.J.; Rostami-Hodjegan, A. Precision dosing to avoid adverse drug reactions. *Ther. Adv. Drug Saf.* **2019**, *10*, 2042098619894147. [CrossRef]
111. Vinks, A.A.; Peck, R.W.; Neely, M.; Mould, D.R. Development and Implementation of Electronic Health Record-Integrated Model-Informed Clinical Decision Support Tools for the Precision Dosing of Drugs. *Clin. Pharmacol. Ther.* **2020**, *107*, 129–135. [CrossRef]

112. Skodvin, B.; Aase, K.; Brekken, A.L.; Charani, E.; Lindemann, P.C.; Smith, I. Addressing the key communication barriers between microbiology laboratories and clinical units: A qualitative study. *J. Antimicrob. Chemother.* **2017**, *72*, 2666–2672. [CrossRef]
113. Darwich, A.S.; Ogungbenro, K.; Vinks, A.A.; Powell, J.R.; Reny, J.L.; Marsousi, N.; Daali, Y.; Fairman, D.; Cook, J.; Lesko, L.J.; 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**, *101*, 646–656. [CrossRef] [PubMed]
114. Abdel-Rahman, S.M.; Breitkreutz, M.L.; Bi, C.; Matzuka, B.J.; Dalal, J.; Casey, K.L.; Garg, U.; Winkle, S.; Leeder, J.S.; Breedlove, J.; et al. Design and Testing of an EHR-Integrated, Busulfan Pharmacokinetic Decision Support Tool for the Point-of-Care Clinician. *Front. Pharmacol.* **2016**, *7*, 65. [CrossRef] [PubMed]
115. Karnik, K. FDA regulation of clinical decision support software. *J. Law Biosci.* **2014**, *1*, 202–208. [CrossRef] [PubMed]
116. Van Lent-Evers, N.A.; Mathot, R.A.; Geus, W.P.; van Hout, B.A.; Vinks, A.A. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: A cost-effectiveness analysis. *Ther. Drug Monit.* **1999**, *21*, 63–73. [CrossRef] [PubMed]
117. Jowett, S.; Bryan, S.; Poller, L.; Van Den Besselaar, A.M.; Van Den Meer, F.J.; Palareti, G.; Shiach, C.; Tripodi, A.; Keown, M.; Ibrahim, S.; et al. The cost-effectiveness of computer-assisted anticoagulant dosage: Results from the European Action on Anticoagulation (EAA) multicentre study. *J. Thromb. Haemost.* **2009**, *7*, 1482–1490. [CrossRef]
118. Rea, R.S.; Capitano, B.; Bies, R.; Bigos, K.L.; Smith, R.; Lee, H. Suboptimal aminoglycoside dosing in critically ill patients. *Ther Drug Monit.* **2008**, *30*, 674–681. [CrossRef]
119. Carlier, M.; Noe, M.; De Waele, J.J.; Stove, V.; Verstraete, A.G.; Lipman, J.; Roberts, J.A. Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients. *J. Antimicrob. Chemother.* **2013**, *68*, 2600–2608. [CrossRef]
120. Roberts, J.A.; Udy, A.A.; Jarrett, P.; Wallis, S.C.; Hope, W.W.; Sharma, R.; Kirkpatrick, C.M.; Kruger, P.S.; Roberts, M.S.; Lipman, J. Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of cefazolin in post-trauma critically ill patients. *J. Antimicrob. Chemother.* **2015**, *70*, 1495–1502. [CrossRef]
121. Nicasio, A.M.; Ariano, R.E.; Zelenitsky, S.A.; Kim, A.; Crandon, J.L.; Kuti, J.L.; Nicolau, D.P. Population pharmacokinetics of high-dose, prolonged-infusion cefepime in adult critically ill patients with ventilator-associated pneumonia. *Antimicrob. Agents Chemother.* **2009**, *53*, 1476–1481. [CrossRef]
122. Beranger, A.; Oualha, M.; Urien, S.; Genuini, M.; Renolleau, S.; Aboura, R.; Hirt, D.; Heilbronner, C.; Toubiana, J.; Treluyer, J.M.; et al. Population Pharmacokinetic Model to Optimize Cefotaxime Dosing Regimen in Critically Ill Children. *Clin. Pharmacokinet.* **2018**, *57*, 867–875. [CrossRef]
123. Georges, B.; Conil, J.M.; Seguin, T.; Ruiz, S.; Minville, V.; Cougot, P.; Decun, J.F.; Gonzalez, H.; Houin, G.; Fourcade, O.; et al. Population pharmacokinetics of ceftazidime in intensive care unit patients: Influence of glomerular filtration rate, mechanical ventilation, and reason for admission. *Antimicrob. Agents Chemother.* **2009**, *53*, 4483–4489. [CrossRef]
124. Shi, Z.R.; Chen, X.K.; Tian, L.Y.; Wang, Y.K.; Zhang, G.Y.; Dong, L.; Jirasomprasert, T.; Jacqz-Aigrain, E.; Zhao, W. Population Pharmacokinetics and Dosing Optimization of Ceftazidime in Infants. *Antimicrob. Agents Chemother.* **2018**, *62*. [CrossRef]
125. Sime, F.B.; Lassig-Smith, M.; Starr, T.; Stuart, J.; Pandey, S.; Parker, S.L.; Wallis, S.C.; Lipman, J.; Roberts, J.A. Population Pharmacokinetics of Unbound Ceftolozane and Tazobactam in Critically Ill Patients without Renal Dysfunction. *Antimicrob. Agents Chemother.* **2019**, *63*, e01265-19. [CrossRef]
126. Garot, D.; Respaud, R.; Lanotte, P.; Simon, N.; Mercier, E.; Ehrmann, S.; Perrotin, D.; Dequin, P.F.; Le Guellec, C. Population pharmacokinetics of ceftriaxone in critically ill septic patients: A reappraisal. *Br. J. Clin. Pharmacol.* **2011**, *72*, 758–767. [CrossRef] [PubMed]
127. Leegwater, E.; Kraaijenbrink, B.V.C.; Moes, D.; Purmer, I.M.; Wilms, E.B. Population pharmacokinetics of ceftriaxone administered as continuous or intermittent infusion in critically ill patients. *J. Antimicrob. Chemother.* **2020**, *75*, 1554–1558. [CrossRef] [PubMed]
128. Khachman, D.; Conil, J.M.; Georges, B.; Saivin, S.; Houin, G.; Toutain, P.L.; Laffont, C.M. Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population

pharmacokinetic-pharmacodynamic analysis and Monte Carlo simulations. *J. Antimicrob. Chemother.* **2011**, *66*, 1798–1809. [CrossRef] [PubMed]

129. Abdul-Aziz, M.H.; Abd Rahman, A.N.; Mat-Nor, M.B.; Sulaiman, H.; Wallis, S.C.; Lipman, J.; Roberts, J.A.; Staatz, C.E. Population Pharmacokinetics of Doripenem in Critically Ill Patients with Sepsis in a Malaysian Intensive Care Unit. *Antimicrob. Agents Chemother.* **2016**, *60*, 206–214. [CrossRef] [PubMed]
130. Ulldemolins, M.; Roberts, J.A.; Wallis, S.C.; Rello, J.; Lipman, J. Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: Special emphasis on unbound pharmacokinetics. *J. Antimicrob. Chemother.* **2010**, *65*, 1771–1778. [CrossRef]
131. Aoyama, T.; Hirata, K.; Hirata, R.; Yamazaki, H.; Yamamoto, Y.; Hayashi, H.; Matsumoto, Y. Population pharmacokinetics of fluconazole after administration of fosfluconazole and fluconazole in critically ill patients. *J. Clin. Pharm. Ther.* **2012**, *37*, 356–363. [CrossRef]
132. Parker, S.L.; Frantzeskaki, F.; Wallis, S.C.; Diakaki, C.; Giamarellou, H.; Koulenti, D.; Karaiskos, I.; Lipman, J.; Dimopoulos, G.; Roberts, J.A. Population Pharmacokinetics of Fosfomycin in Critically Ill Patients. *Antimicrobial. Agents Chemother.* **2015**, *59*, 6471–6476. [CrossRef]
133. Krens, S.D.; Hodiamont, C.J.; Juffermans, N.P.; Mathot, R.A.A.; van Hest, R.M. Population Pharmacokinetics of Ganciclovir in Critically Ill Patients. *Ther. Drug Monit.* **2019**, *42*, 295–301. [CrossRef]
134. De Velde, F.; de Winter, B.C.M.; Neely, M.N.; Yamada, W.M.; Koch, B.C.P.; Harbarth, S.; von Dach, E.; van Gelder, T.; Huttner, A.; Mouton, J.W. Population Pharmacokinetics of Imipenem in Critically Ill Patients: A Parametric and Nonparametric Model Converge on CKD-EPI Estimated Glomerular Filtration Rate as an Impactful Covariate. *Clin. Pharmacokinet.* **2020**. [CrossRef] [PubMed]
135. Roberts, J.A.; Cotta, M.O.; Cojutti, P.; Lugano, M.; Rocca, G.D.; Pea, F. Does Critical Illness Change Levofloxacin Pharmacokinetics? *Antimicrobial. Agents Chemother.* **2016**, *60*, 1459–1463. [CrossRef] [PubMed]
136. Soraluce, A.; Barrasa, H.; Asin-Prieto, E.; Sanchez-Izquierdo, J.A.; Maynar, J.; Isla, A.; Rodriguez-Gascon, A. Novel Population Pharmacokinetic Model for Linezolid in Critically Ill Patients and Evaluation of the Adequacy of the Current Dosing Recommendation. *Pharmaceutics* **2020**, *12*, 54. [CrossRef]
137. Crandon, J.L.; Ariano, R.E.; Zelenitsky, S.A.; Nicasio, A.M.; Kuti, J.L.; Nicolau, D.P. Optimization of meropenem dosage in the critically ill population based on renal function. *Intensive Care Med.* **2011**, *37*, 632–638. [CrossRef] [PubMed]
138. Braune, S.; Konig, C.; Roberts, J.A.; Nierhaus, A.; Steinmetz, O.; Baehr, M.; Kluge, S.; Langebrake, C. Pharmacokinetics of meropenem in septic patients on sustained low-efficiency dialysis: A population pharmacokinetic study. *Crit Care* **2018**, *22*, 25. [CrossRef]
139. Rapp, M.; Urien, S.; Foissac, F.; Beranger, A.; Bouazza, N.; Benaboud, S.; Bille, E.; Zheng, Y.; Gana, I.; Moulin, F.; et al. Population pharmacokinetics of meropenem in critically ill children with different renal functions. *Eur. J. Clin. Pharmacol.* **2020**, *76*, 61–71. [CrossRef]
140. Maseda, E.; Grau, S.; Luque, S.; Castillo-Mafla, M.-P.; Suárez-de-la-Rica, A.; Montero-Feijoo, A.; Salgado, P.; Gimenez, M.-J.; García-Bernedo, C.A.; Gilsanz, F.; et al. Population pharmacokinetics/pharmacodynamics of micafungin against Candida species in obese, critically ill, and morbidly obese critically ill patients. *Crit. Care* **2018**, *22*, 94. [CrossRef]
141. Felton, T.W.; Roberts, J.A.; Lodise, T.P.; Van Guilder, M.; Boselli, E.; Neely, M.N.; Hope, W.W. Individualization of piperacillin dosing for critically ill patients: Dosing software to optimize antimicrobial therapy. *Antimicrobial. Agents Chemother.* **2014**, *58*, 4094–4102. [CrossRef] [PubMed]
142. Sandri, A.M.; Landersdorfer, C.B.; Jacob, J.; Boniatti, M.M.; Dalarosa, M.G.; Falci, D.R.; Behle, T.F.; Bordinhao, R.C.; Wang, J.; Forrest, A.; et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: Implications for selection of dosage regimens. *Clin. Infect Dis.* **2013**, *57*, 524–531. [CrossRef] [PubMed]

143. Sime, F.B.; Byrne, C.J.; Parker, S.; Stuart, J.; Butler, J.; Starr, T.; Pandey, S.; Wallis, S.C.; Lipman, J.; Roberts, J.A. Population pharmacokinetics of total and unbound concentrations of intravenous posaconazole in adult critically ill patients. *Crit. Care.* **2019**, *23*, 205. [CrossRef] [PubMed]
144. Xie, J.; Roberts, J.A.; Alobaid, A.S.; Roger, C.; Wang, Y.; Yang, Q.; Sun, J.; Dong, H.; Wang, X.; Xing, J.; et al. Population Pharmacokinetics of Tigecycline in Critically Ill Patients with Severe Infections. *Antimicrobial. Agents Chemother.* **2017**, *61*, e00345-17. [CrossRef] [PubMed]