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Clinical Pharmacy-Driven Optimization OF Antimicrobial Therapy IN Drug-Resistant Infections Considering Host Pharmacokinetic Variability

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Abstract
Antimicrobial resistance (AMR) is an increasing health challenge in the world, especially among patients with severe health problems who are infected with multidrug resistant organisms (MDROs). The altered pharmacokinetics (PK) in these patients may not respond to standard antimicrobial treatment because of dysfunction of the organs, hypoalbuminemia as well as fluid shifts. This poses a major problem of maximizing the use of antimicrobial therapy to achieve adequate exposure of the drug at the point of infection. One potential mode of improving therapeutic outcomes is through clinical pharmacy interventions especially those that are supported by pharmacokinetic/pharmacodynamic (PK/PD) principles. Such interventions are individual dosing schedules and therapeutic drug monitoring (TDM), that is, it considers the physiological changes and infection dynamics of the patient. Critical is the necessity of the accurate dose, under-dose may cause the failure of treatment and the rise of additional resistance, whereas over-dose may cause toxicity. This review takes a complex look at drug resistance, host pharmacokinetic variability, and how clinical pharmacy can be useful in optimizing antimicrobial treatment. It highlights the need to use individualized dosing in enhancing treatment efficacy and minimize the occurrence of resistance. Furthermore, it contributes to the inclusion of sophisticated pharmacokinetic and TDM models into the standard of clinical practice to ensure the best therapeutic use of critical patients.

Keywords Antimicrobial resistance (AMR); Pharmacokinetics (PK); Therapeutic drug monitoring (TDM); Multidrug-resistant organisms (MDRO); Personalized dosing.

Introduction

Antimicrobial resistance (AMR) is a serious microbial infection and by 2019, AMR had led to 4.95 million infections and 1.27 million deaths (Hommes and Surewaard, 2022). Without implementing any measures to curb the emergence of AMR, 10 million AMR-related deaths are predicted annually by 2050 (Ghanem, 2020). On the eve of this crisis, the world is in critical need of guidelines to surmount the most stubborn pathogens and maximize the existing levels of antimicrobial usage (Ostyn et al., 2024). It involves the use of antimicrobial drugs and balancing the four-core pharmacokinetics (ADME) of Absorption, Distribution, Metabolism, and Elimination) and the four core pharmacodynamics to

minimize collateral damage. It is even more complicated with high-acuity patients due to the fact that the standard protocols are based on an assumption of a particular physiology of patient and do not consider that critically ill patients may have gross changes to their drug ADME (Huang et al., 2024). In such situations, regular protocol-based antimicrobial therapy predisposes patients to high chances of under-therapeutic concentration of the chosen antibacterials. This implies that the need to implement antimicrobial therapy into the fray of clinical pharmacy is necessary to offer more personalized, antipseudomonal/pseudomonas, and patient-specific antimicrobial therapy (Onita et al., 2025).

Critically ill patients can have poor drug exposure because of inter-patient variability, increased risk of treatment failure, and adverse drug reactions (Pea, 2022). Regarding antibiotic resistance and tolerance, resistance can be defined as the capability of bacteria to grow in the presence of the antibiotic, whereas tolerance can be defined as the capability of the bacteria to survive multiple antibiotics, and the periods in which this can happen are indefinable, thus contributing to the risk of developing resistance (Fisher et al., 2017; Lu et al., 2025). Considering the challenges mentioned above, there is a need to streamline antibiotic therapy to ensure that it entails the principles of pharmacodynamics and pharmacokinetics. The principles of pharmacodynamics and pharmacokinetics have been attributed to better antibiotic effects and decreased antibiotic resistance since the 1970s (Alikhani et al., 2025; Bulman et al., 2022). According to the available literature, in critical care, patients often have juddering kinetic parameters, which are mainly represented by disrupted drug distribution (i.e., increased volume of distribution (VOD)) and slow (i.e., unpredictable) drug clearance (Povoa et al., 2021). The merit of clinical pharmacists, as a result of their knowledge of the virtue of individual dosing, in this situation, is splendidly ascribed to the art of precise dosing and to the development of traditional science, in order to provide the maximum dosage exposure to the site of infection (Ha et al., 2017). Such personalized standard scientific practice is an effort to overcome the scientific imprecision of population dosing, resulting in a championing of sub-therapeutic dosing (i.e., the promotion of resistance and treatment failure) or a championing of supra-therapeutic dosing (i.e., increased toxicity and collateral damage) (Bhandari et al., 2023; Roggeveen et al., 2022). In addition, the science of survival (i.e., heightened mortality and inability to treat the patient) is linked to subtherapeutic dosing, specifically the most sensitive south of the causal barrier, in critically ill patients (Yow et al., 2022).

Overview of Drug-Resistant Infectious Diseases Multidrug-resistant pathogens (MDRO such as s)

Carbapenem-resistant Enterobacteriaceae, vancomycin-resistant Enterococci, and methicillin-resistant Staphylococcus aureus are among the resistant pathogens that pose challenges to humans owing to their resistance mechanisms, morbidity, and mortality rates (Roberts et al., 2014). Such infections demand novel solutions, especially combinations of antibiotics and novel methodologies that entail the pharmacodynamics and pharmacodynamics of antibiotics (Abdul-Aziz et al., 2015). These measures encompass optimizing the antibiotic regime, depending on the specifics of the antibiotics, the sensitivity of the pathogen, and the physiology of the host, thus reaching the best concentration of the antibiotic in the area of infection (Ture et al., 2025). The necessity to use existing antibiotics cannot be attributed without the creation of new strategies to address the urgent global health challenge of antibiotic resistance caused by multidrug-resistant pathogens (Abdul-Aziz et al., 2015). When strains of infection become resistant, the contribution of clinical pharmacy becomes of primary importance, and the effects of resistant strains are reduced through the optimization of antimicrobial therapy for a single infection and patient (Zhou et al., 2023).

The presence of a single subpopulation of bacteria that is not only phenotypically and functionally antibiotic-resistant but also possibly in vivo and antibiotic-resistant but in vitro-susceptible makes successful treatment more difficult and makes more rigid clinical trials necessary (Fisher et al., 2017; Kuehl et al., 2019). Some of the difficulties posed by critically ill patients include increased MICs of carbapenems against gram-negative isolates, which are almost four to eight times higher in critically ill patients than in non-critically ill patients. This is a depiction of the urgent need for better PK/PD-informed dosing systems (Roberts et al., 2014). These complicated microbial adaptations indicate that, accompanied by resistance, the adaptation of microbes entails novel dynamics beyond survival tactics (Song et al., 2021). One of them is Klebsiella pneumoniae, which has demonstrated more than 70 per cent global resistance to antibiotics, and its drivers, such as ESBLs and carbapenemases, result in high

mortality and bloodstream infections, along with the emergence of hypervirulent strains (Bouhrour et al., 2024).

The mechanisms of resistance which influence pharmacotherapy

There are several mechanisms by which bacterial pathogens can resist antimicrobials among them being enzymatic degradation, target modification, efflux pumps and reduced membrane permeability; all of which can influence both the pharmacodynamics of response and the effectiveness of treatment. (Soni et al., 2024). An example of these is K. pneumoniae, which is antifungally resistant and is one of the deadliest groups of pathogens. K. pneumoniae antimicrobial resistance how pathogens develop multiple resistance against antifungals using devel portion of mobile genetic resources, and estimating the mortality rate Dobreva et al., 2022). Several extensively unresponsive and pan unanswerable pathogens, with drug therapies as an initial step, and the assumption of endless hypothesized and unreasonably irrational and novel antibiotic actions and therapies, such as compound therapy and non-antibiotic actions, all targeting the radical purpose of avoiding therapeutic failure and maximization of drug-resistant pathogens. The interaction between the organism resistance mechanisms and the pharmacokinetics of the host adds to the complex nature of therapeutic success (Kadirvley et al., 2019, Maji et al., 2024). This highlights the defensive requirements of full susceptibility profiling, MIC, MICHI, and MPC to provide a sufficient assessment of the bacterial resistance profile. (Golitova et al., 2023). The emergence of gram-negative multidrug- and carbapenem-resistant bacteria, such as Pseudamonas asruginosa, Acinetobacter baumanni, and Stenotrophomonas maltophania, has further complicated the provision of the most appropriate antimicrobial treatment (Chen et al., 2025).

Host pharmacokinetic variability in infections

The changes in the physiology of critically ill individuals, such as fluid shifts, hypoalbuminemia, and organ dysfunction, significantly influence the pharmacokinetics of drugs, resulting in unpredictable plasma concentrations and nonoptimal treatment. These changes require personalized dosing, especially in the case of renally excreted antibiotics, to ensure the prevention of underdose exposure, leading to resistance and toxicity that cause adverse drug events (Karukappadath et al., 2023). In particular, the indicators of sepsis and septic shock are characterized by notable shifts in drug absorption, distribution, metabolism, and excretion, which directly affect the disposition of antimicrobial agents and make it difficult to achieve therapeutic targets (Howden et al., 2023).

For example, a higher level of cardiac output and capillary permeability in patients with septic shock may mean that hydrophilic antibiotics have a greater volume of distribution than expected in plasma (Karukappadath et al., 2023). However, acute kidney damage or hepatic dysfunction, which usually occurs in severe infections, may decrease drug elimination, thereby cause drug retention and increase the chances of toxicity (Tao et al., 2025). Such pharmacodynamic alterations highlight the importance of therapeutic drug monitoring and dose optimization techniques that will provide sufficient drug exposure, which will reduce adverse events in a highly heterogeneous patient population. Additionally, antibiotic pharmacokinetic variability, mainly due to alterations in renal clearance and adjustments in the volume of distribution of hydrophilic antibiotics, usually makes the process of optimum dosing prediction difficult (Roberts et al., 2019).

This variability is especially high in critically ill patients, in whom altered renal clearance, increased extravascular distribution, and augmented renal clearance may dramatically influence antibiotic exposure and therapeutic efficacy (Corona et al., 2023). Indeed, the elevated distribution volumes and increased renal clearance in critically ill patients, especially those with sepsis, may be associated with subtherapeutic antibiotic levels, resulting in the need to increase the dose to reach the desired pharmacodynamic/pharmacokinetic levels (Pea, 2022). Such physiological changes, including fluid resuscitation, hypoalbuminemia, and endothelial dysfunction, are all predictors of an increased interstitial space, specifically for hydrophilic antimicrobial agents (Moniz et al., 2020). Consequently, the usual administration systems of antibiotics, which are usually based on investigations performed with healthy participants, often do not reach sufficient levels of antimicrobial action at the infected location in critically ill patients experiencing sepsis (Coopersmith et al., 2018; Hites, 2021). The achievement of optimum drug exposure in this susceptible group is further complicated by the presence of pharmacokinetic variability caused by factors such as changes in cardiac output, tissue perfusion, and end-organ dysfunction (Felton et al., 2014; Shah et al., 2015).

Effects of severe disease and dysfunction of organs, and inflammation

Altered pharmacokinetics is common in critically ill patients because of reasons like increased antibiotic-free-fraction attributed to hypoalbuminemia, expanded volume of distribution, hepatic or renal dysfunction, which undermine the effective delivery of antimicrobials (Ramos et al., 2023). Drastic fluid losses and organ dysfunction in sepsis may result in augmented renal clearance, which may result in subtherapeutic levels of renally cleared drugs (Onufrak et al., 2016). This enhanced renal clearance, which is not always related to increased mortality, may reduce the effectiveness of antibiotics, particularly hydrophilic ones, because it eliminates them rapidly from systemic circulation (Burnham et al., 2017; Onufrak et al., 2016). This tendency is very typical among younger and less comorbid patients with septic events, which underlines the complexity of the targeted exposure to antibiotics and requires close attention to renal function (Burnham et al., 2017). In addition, the disposition of antimicrobial agents in patients with critical illnesses is variable because of several interrelated factors, including physiological alterations that influence drug absorption, distribution, metabolism, and excretion (Tanaka, 2025).

In particular, there is a high probability of critical patients (primarily sepsis) to have a high fluid shift and hypoalbuminemia, which might augment the quantity of circulation of a hydrophilic antimicrobial, thus resulting in subtherapeutic concentrations in the case of the use of a regular dosing routine (Bhandari et al., 2023). Moreover, acute kidney injury and dysfunction of other organs may reduce drug clearance, resulting in accumulation and the risk of toxicity (Aroca-Martine et al., 2022). On the other hand, augmented renal clearance, which may be associated with critically ill patients, may result in increased drug clearance, which causes therapeutic drugs to be eliminated faster, requiring extra or increased dosing rates to sustain drug levels (Burnham et al., 2017). The heterogeneity of antibiotic pharmacokinetics can result from these complicated physiological modifications in critical illness, especially sepsis, and make it difficult to achieve optimal drug exposure and predispose it to therapeutic failure and drug toxicity (Fawaz et al., 2020; Roberts et al., 2014).

This problem is complicated by the fact that optimal pharmacodynamic targets are not always met in critically ill patients, and it is necessary to report significant differences in antibiotic concentrations (Roggeveen et al., 2019). These deviations in the target concentrations may lead to either under pathogen eradication or a higher risk of adverse drug reactions, which is why the need to use an individualized antimicrobial dosing strategy is extremely important in this vulnerable group (Gatti & Pea, 2021). Furthermore, the increased distribution of most antibiotics directly correlates with the rise in severity of morbidity, and unless this is considered, it may lead to inadequate concentration in the early days of therapy (Roberts et al., 2014). This highlights the urgency of tailored dosing systems of antibiotics and consideration of individual pharmacokinetic changes in each critically ill patient to guarantee sufficient drug exposure and maximize treatment effectiveness (Roberts et al., 2014).

Individualized dosing regimens play a significant role in maximizing the efficacy of antimicrobial therapy among critically ill patients with drug-resistant infections because these patients demonstrate significant pharmacokinetic heterogeneity. These interventions play a crucial role in meeting certain pharmacokinetic/pharmacodynamic goals, which guarantee the development of therapeutic efficacy and reduce the chances of resistance (Cortegiani et al., 2023; Williams et al., 2023). These personalized changes are especially relevant because improper dosing may cause unfavorable results in patients with severe conditions, and careful consideration of patient-specific determinants of drug disposition is necessary (Póvoa et al., 2021). For example, vancomycin, an antimicrobial used for severe drug-resistant infections, frequently necessitates increased doses (up to 34 g/day) in patients with normal renal function to reach target area under the curve/minimum inhibitory concentration ratios, which underlines the necessity of a personalized regimen as opposed to standardized regimens (Liu et al., 2011). The essential requirement is therapeutic drug monitoring, which can guide such changes, especially for drugs such as vancomycin, aminoglycosides, and beta-lactams, to achieve optimal drug exposure and reduce toxicity in critically ill patients (Tanaka, 2025). This personalization is further applied to the proper concentrations of agents such as meropenem and piperacillin/tazobactam, in which pathogen susceptibility and renal function play critical roles in determining the dosing regimen (Weinelt et al., 2022).

These targeted treatments are enhanced by the role of clinical pharmacists in critical care units in real-time adaptations, considering patient-specific pharmacokinetic values and clinical responses (Póvoa et

al., 2021). These evidence-based interventions, which involve drug level monitoring and dosage adjustments, take precedence to maximize the chances of a successful therapeutic process and reduce the development of further resistance in the demanding conditions of critical care (Al-Shaer et al., 2025). These initiatives are especially important in the management of multidrug-resistant bacterial infections, in which standard dosing might not reach therapeutic goals, thus leading to treatment failures and resistance spread (Brink et al., 2020; Timsit et al., 2019). Optimization of the renal and hepatic dose: Owing to the significant importance of renal and hepatic clearance and disposal of drugs, the optimal dosages of antimicrobials set within these parameters are core to the preventions under- and over-dose effects (Saito et al., 2019). This is especially relevant to critically ill patients who commonly have different physiological conditions, such as variable renal and hepatic clearance, which require dynamic dose changes (Saito et al., 2019; Zilahi et al., 2016). For example, hydrophilic and renally excreted, moderately lipophilic antimicrobials run the risk of significant changes in plasma concentration per day in critically ill patients because of changes in extracellular fluid volume and renal or liver performance (Russo et al., 2023).

Table 1: Overview of Key Antimicrobial Resistance (AMR) Pathogens.

Pathogen	Resistance Mechanisms	Challenges
Carbapenem-resistant Enterobacteriaceae (CRE)	Carbapenemase production, efflux pumps, decreased membrane permeability	High mortality, limited treatment options, widespread resistance
Vancomycin-resistant Enterococci (VRE)	Target modification (D-Ala-D-Ala to D-Ala-D-Lac), efflux pumps	Challenging to treat with common antibiotics, widespread resistance
Methicillin-resistant Staphylococcus aureus (MRSA)	Altered penicillin-binding proteins (PBPs), beta-lactam resistance	Persistent infections, difficult to treat with beta-lactams
Klebsiella pneumoniae	ESBL production, carbapenemase production (e.g., KPC)	Resistance to beta-lactams, carbapenems, high mortality rate
Pseudomonas aeruginosa	Efflux pumps, beta-lactamase production, altered porin channels	Biofilm formation, resistance to multiple antibiotics

Thus, accurate evaluation of renal and hepatic function in conjunction with constant assessment is of primary importance in terms of adjusting the dose appropriately to attain therapeutic drug concentrations without causing toxicity (Lam et al., 2017). For example, anti-tuberculosis drugs must be optimally used based on renal function, which means that their dosage should vary across patients with chronic kidney disease (Saito et al., 2019). Renal replacement therapy should be considered carefully in cases of possible acute kidney injury, which is frequently aggravated by sepsis or nephrotoxic medication, as it substantially changes the extent of drug clearance and requires additional changes in dosage to avoid the effects of drug accumulation or underexposure (Elias Pinheiro et al., 2019; Pampa-Saico et al., 2020). Monitoring of hepatic function is also critical, particularly when drugs are metabolized by the liver, where defective functioning results in subsequent delayed drug clearance and toxicity, thus requiring dose adjustments to prevent adverse events.

Moreover, when working with drugs such as colistimethate sodium, it is mandatory to measure and monitor drug concentrations to create a proper dose, thus alleviating the emergence of resistance and nephrotoxicity (Pampa-Saico et al., 2020). This holistic strategy for renal and hepatic dose optimization constitutes a pillar of personalized antimicrobial stewardship, which guarantees effective therapy and reduces drug-related toxicities in patient populations with numerous intricacies (Saito et al., 2019). Therefore, the repetitive review of antimicrobial regimens, especially those that are excreted mainly through the urine, is crucial for critically ill patients, as changes in pathophysiology may quickly become apparent regarding drug disposition (Pea & Viale, 2009).

Therapeutic drug monitoring (TDM) is necessarily when customizing antimicrobial therapy, especially in patients with critical illnesses with significant pharmacokinetic variability is possible to adjust the

dose ideal time me to achieve optimal drug exposure and clinical outcomes (Gatti et al., 2021; Schmid et al., 2023). This mechanism maintains antibiotic concentrations within the therapeutic window, maximizing bacterial death and reducing toxicity (Gatti et al., 2022). This is especially important for antimicrobials with a low therapeutic index or those with concentration-dependent potency and toxicity, including aminoglycosides and vancomycin, where accurate dosage is essential to achieve a successful response and prevent adverse effects on the patient (Ture et al., 2025).

In the case of concentration-dependent antimicrobials, such as aminoglycosides or colistin, higher dosages might be required to reach the pharmacodynamic targets, which is often informed by therapeutic drug monitoring (Pampa-Saico et al., 2020; Timsit et al., 2014). In addition, time-dependent antimicrobials, including beta-lactams, can be optimized by therapeutic drug monitoring to determine the duration of time when the drug concentration is above the minimum to activate inhibition (Wunderink et al., 2020). Therefore, TDM is gaining momentum to optimize the doses of antibiotics, particularly in severe infections, beyond its classical role of toxicity minimization to actively promote the therapeutic effect (Wong et al., 2014). This individual strategy is especially critical in cases of augmented renal clearance, whereby typical dosing can cause subtherapeutic concentrations, thus requiring an increase in doses or extended infusions, as suggested in the case of novel combinations of beta-lactam and beta-lactamase inhibitors (Gatti & Pea, 2021). Moreover, TDM is critical for detecting patients at risk of toxicity due to excessive drug exposure, particularly with drugs with narrow therapeutic indices (Abdul-Aziz et al., 2020; Wong et al., 2014).

Antimicrobial Classes and PK Challenges

b-lactams, glycopeptides, aminoglycosides and antifungals. These ese varied classes of antimicrobial pose different pharmacodynamics and pharmacokinetic and they require careful keen attention to achieve good clinical outcomes. An example of this is b-lactams, which have time-dependent killing activity and may require a longer or continuous infusion to sustain levels above the minimum inhibitory concentration over a sufficient period to ensure maximum bactericidal activity (Introna et al., 2025). However, the complex pharmacokinetic properties and the likelihood of nephrotoxicity mean that therapeutic drug monitoring is often necessary to achieve effective peak levels of glycopeptides, such as vancomycin, and minimize side effects (Mabilat et al., 2019; Yow et al., 2022).

Table 2: Pharmacokinetic (PK) Variability in Critically Ill Patients.

Physiological Change	Impact on Pharmacokinetics (PK)	Effect on Drug Therapy
Fluid Shifts (e.g., edema, dehydration)	Changes in drug volume of distribution (VOD)	Increased VOD for hydrophilic drugs, requiring higher doses
Hypoalbuminemia	Decreased protein binding of drugs	Higher free drug concentration, potential for increased toxicity
Organ Dysfunction (e.g., liver, kidney)	Altered drug clearance (reduced or enhanced)	Risk of drug accumulation (toxicity) or sub-therapeutic levels
Sepsis/Septic Shock	Increased cardiac output, altered tissue perfusion	Greater distribution of hydrophilic drugs, unpredictable drug levels
Renal Failure	Decreased renal clearance of renally excreted drugs	Risk of drug accumulation, requiring dose adjustments

The ratio of area under the curve and minimum inhibitory concentration (AUC/MIC) has the highest correlation with vancomycin efficacy, with targets above 400 in terms of better clinical response and microbiological eradication (Liu et al., 2011). However, aminoglycosides are concentration-dependent bactericidal agents, and the maximization of peak concentrations per MIC (Cmax/MIC) is essential to achieve the desired effect, which frequently results in once-daily dosing regimens to take advantage of post-antibiotic effects and minimize nephrotoxicity (Onufrak et al., 2016; Roberts et al., 2011). Although trough monitoring of vancomycin is a standard practice, especially in acute infections, critical patients, or those with impaired renal clearance, exclusive use of the metric to optimize the dose may not be adequate to achieve accuracy in the dose and usually takes time to reach the therapeutic threshold (Liu et al., 2011; Yow et al., 2022). This weakness demonstrates the necessity of more profound

pharmacokinetic studies and sophisticated modeling methods to personalize the dosage of vancomycin and to leave behind conventional trough-based dosing strategies (Liu et al., 2011; Mabilat et al., 2019). Historical trends in the development of vancomycin-related therapeutic drug monitoring have led to model-inspired precision dosing regimens that combine the application of Bayesian predictions to achieve optimal area under the curve goals faster and more dependably (Yow et al., 2022).
This will reduce the risk of nephrotoxicity due to sustained supratherapeutic levels and maximize the destruction of bacteria, especially in difficult-to-treat infections (Wynsberge et al., 2024). Moreover, vancomycin bone penetration is overall good but with a high level of variability, with bone: plasma ratios between 0.05 and 0.97 and intracellular accumulation ratios of 6.3 to 344.74 (Zelmer et al., 2022). The significance of this wide range is that it is important to consider the tissue-specific pharmacokinetics when treating deep-seated infections. The activity of vancomycin in biofilm-associated infections, particularly with Staphylococcus aureus and Staphylococcus epidermidis, has been reported to be variable, with certain studies showing the ability of more recent agents, such as dalbavancin, to be more effective in controlling biofilm-embedded microbes (Oliva et al., 2021).

Attainment of the intended pharmacokinetic/pharmacodynamic (PK/PD) endpoint of vancomycin, or an area under the curve in 24 hours (AUC24h) to minimum inhibitory concentration ratio of 400-600 mg x h,/L is essential for the efficacy and safety of the agent, assuming an MIC of mg/L/L of the agent in empirical therapy (Rio-No et al., 2023; Xu et al., 2025). However, there are indications that the attainment of such a target when using conventional dosing regimens is not always consistent, leading to either suboptimal exposure or nephrotoxicity (Song et al., 2024; Stocker et al., 2020). This highlights the need for personalized dosing plans, which may be informed by model-based therapeutic drug monitoring, to maximize patient outcomes and reduce adverse events, especially in critically ill populations (Gastmans et al., 2022; Sulaiman et al., 2021).
Another strong approach to predicting future drug exposure and optimizing vancomycin dosing to consistently achieve therapeutic targets is based on population pharmacokinetic models combined with individual patient data, commonly called Bayesian forecasting (Gastmans et al., 2022). This sophisticated method is opposed to classical single-point trough monitoring, which has been proven to be less efficient in forecasting total drug exposure and clinical outcomes (Giuliano et al., 2009; Song et al., 2024). The vancomycin pharmacokinetic problem is also worsened by the fact that penetration into various sites of infection differs, and the target AUC0-24/MIC of 1000 is given to lung interstitial fluid and cerebrospinal fluid, whereas lower values are used in the sternal bones, capsular tissue, pleural fluid, bloodstream, and pericardium (Song et al., 2021). Such inconsistency requires a more subtle method of achieving targeted results, in which patient-specific dosing schedules are selected based not only on patient-specific pharmacokinetic characteristics but also on the location of infection (Giuliano et al., 2009).
Although essential for treating infections caused by gram-positive organisms, such as Methicillin-resistant Staphylococcus aureus, the use of vancomycin is complicated by its nephrotoxicity, the risk of resistance with repeated use, its limited ability to penetrate cells, and the possibility of having staphylococcal reservoirs in vivo (Granell et al., 2017; Surewaard et al., 2016). These intracellular reservoirs, especially in macrophages and renal cells, may provide a haven for S. aureus, making it difficult to eliminate and causing lasting infections despite the administration of vancomycin throughout the system (Surewaard et al., 2016). Moreover, the dosing schedule of vancomycin is further complicated by the artificial consistency of 400 as the AUC24/MIC of vancomycin, which is highly likely to be found in the artificial target of MRSA bloodstream infections and may not be applicable to all types of infections and patients (Song et al., 2024).
This will require the reconsideration of target parameters depending on the particular type of infection and patient demands to achieve the best therapeutic results (Liu et al., 2011). The nature of vancomycin pharmacodynamics, especially in critically ill patients, can frequently lead to the need to use Bayesian forecasting methods to predict AUC more accurately, despite the fact that the existing software might be based on simplified one-compartment models (Stocker et al., 2020). Despite these developments, there are knowledge gaps regarding the most suitable method to maximize vancomycin therapy and reduce toxicity, despite decades of clinical use of the drug (Rybak et al., 2020). This inconsistency underlines the necessity of studies on individual dosing approaches that consider the individual differences of patients and the peculiarities of their infections (Marko et al., 2021; Song et al., 2021).

Nevertheless, the development of vancomycin resistance and the difficulty in removing the infection after entering cells, including macrophages and renal cells, complicate the treatment process further, which requires new solutions to increase the delivery and efficacy of antibiotics (Surewaard et al., 2016; Zelmer et al., 2022).

Table 3: Clinical Pharmacy Interventions for Optimizing Antimicrobial Therapy.

Intervention	Antimicrobial Agent	Purpose/Effect
Therapeutic Drug Monitoring (TDM)	Vancomycin, aminoglycosides, beta-lactams	Optimize drug exposure, reduce toxicity, and prevent resistance
Personalized Dosing (PK/PD-guided)	Vancomycin, meropenem, piperacillin/tazobactam	Ensure appropriate drug concentrations based on patient-specific PK profiles
Bayesian Forecasting	Vancomycin, aminoglycosides	Predict optimal dosing to achieve target AUC/MIC ratios faster
Clinical Pharmacy Consultations	General (various antimicrobials)	Provide individualized dosing regimens based on drug monitoring data
Implementation of AUC-guided Dosing Protocols	Vancomycin, meropenem	Achieve desired pharmacokinetic targets for optimal efficacy and safety

Clinical Pharmacy Interventions and Outcomes

Clinical research literature shows that clinical pharmacy interventions, especially those based on pharmacokinetic/pharmacodynamic concepts, can greatly enhance patient outcomes by optimizing the exposure too vancomycin (Claeys et al., 2020). Pharmacist-directed collaborative practice models have been shown to improve vancomycin dosing in the intensive care unit, resulting in high-quality treatment outcomes (Levin et al., 2016). This optimization involves fewer cases of vancomycin-associated nephrotoxicity and retains the efficacy of the treatment in patients with methicillin-resistant Staphylococcus aureus bacteremia (Song and Han, 2022). These interventions frequently include close vancomycin level monitoring and modification of the dosing schedule with regard to the particular patient factors and response beyond the trough-only monitoring to advanced AUC-driven approaches (Komoto et al., 2018). These AUC-controlled measures are not only logistically demanding but also extremely important for achieving optimal bactericidal activity with the least risk of nephrotoxicity (Marko et al., 2021).

The duration of treatment with vancomycin and the timeliness of pharmacist interventions also impact outcomes, and early and regular monitoring can be useful in preventing nephrotoxicity (Maji et al., 2019; Sugita et al., 2023). Moreover, it is also demonstrated that expanded pharmacy practice models have a positive impact on the use of vancomycin loading doses and maintenance doses, especially in intensive care unit patients, which, in turn, results in enhanced patient safety outcomes in the form of a significant decrease in vancomycin-associated nephrotoxicity (Han et al., 2017). These results highlight the importance of pharmacists in maximizing the use of vancomycin, ensuring that patients receive the right and effective antimicrobial interventions, and reducing the risk of adverse drug events. This fact is one of the reasons why the inclusion of clinical pharmacists in antimicrobial stewardship programs should be considered to increase the accuracy of vancomycin administration and monitoring (Rybak et al., 2020).

Effects on efficacy, toxicity, and resistance prevention. The adoption of modern pharmacokinetic modeling into practice, especially Bayesian approaches to dosing with AUC, has been shown to enhance the therapeutic efficacy of vancomycin decrease the occurrence of acute kidney injury (Claeys et al., 2020; Han et al., 2017). This makes it more precise and enables individual dosing that seeks to ensure maximum exposure to bacteria but does so cautiously because vancomycin has a very narrow therapeutic index (Komoto et al., 2018). Furthermore, the discontinuation of conventional trough-based dosing with the aid of consensus principles and the transition to AUC-guided dosing have demonstrated opportunities to reduce nephrotoxicity rates in adult patients who take vancomycin for all indications (Robinson et al., 2023). Nonetheless, there are challenges associated with the practical application of

AUC-guided dosing, such as the availability of special software, trained staff, and strong laboratory facilities to measure drug levels accurately and on time (Baiocco et al., 2023; Han et al., 2017).
Nevertheless, research has shown that AUC/MIC-driven pharmacy-based dosing protocols of vancomycin can reduce the incidence of acute kidney injury by a large margin relative to trough-based dosing protocols (Marović et al., 2025; Phillips et al., 2023). These modern measures can lead to improved patient outcomes across all three aspects, enhancing therapeutic concentrations by improving intra-consistency to improve antimicrobial efficacy, and potentially reducing the emergence of resistance (Firman et al., 2022). Moreover, these optimized dosing regimens, particularly loading doses, have been associated with a faster acquisition of therapeutic concentrations and negative conversion in cases of MRSA bacteremia, leading to better patient outcomes (Lee et al., 2024). Such preventive measures are crucial, especially considering the problems of intracellular bacterial infections, as the penetration of vancomycin into host cells is minimal; hence, the importance of continuing therapeutic levels of the drug at the point of infection (Surewaard et al., 2016). This shortcoming mandates the development of new methods, which might entail the incorporation of combination therapy or the development of new drug delivery vectors, to address the obstacles to intracellular activity (Zelmer et al., 2022). For example, nanoparticles and vancosomes loaded with vancomycin have both elevated intracellular penetration and efficacy against *S. aureus* in osteoblast models and in vivo, respectively, demonstrating promising prospects for better treatment of difficult-to-reach infections (Surewaard et al., 2016; Zelmer et al., 2022). These nano medicinal platforms represent a significant paradigm shift in the fight against antibiotic-resistant bacteria, such as MRSA, as they can deliver a targeted product and exhibit better intracellular activity, which is often lacking in traditional therapies (Nandhini et al., 2022; Surewaard et al., 2016).

Challenges and Implementation Barriers

Advanced pharmacodynamics/pharmacokinetic technics, such as AUC-guided dosing and nanoparticle-mediated delivery are difficult to implement a resource-limited environments because of their high cost (specialized software, laboratory equipment, trained persons, etc.) (Chander et al., 2024; Hommes and Surewaard, 2022). These advanced systems may be costly to install initially, which is prohibitive for most healthcare establishments, especially those in the developing world (Bradley & Ng, 2023). Additionally, real-time monitoring of drug levels and computational models are not easily available, which may hinder the timely modification of the antibiotic regimen and thus frustrate patient outcomes (Schneider et al., 2023).
This is complicated by the fact that not all pharmacists and infectious disease experts are skilled enough to interpret complex pharmacokinetic data and create individual dosing changes, thus limiting the extensive use of these advanced practices (Giuliano et al., 2009). Furthermore, the problem of managing the variable pharmacokinetic profile of patients in a critical care setting, particularly regarding medications such as vancomycin, can also be partially explained by the fact that the presence of specialized expertise and efficient monitoring systems, which are often not available in resource-limited settings, is essential (Song and Han, 2022). As a result, the healthcare infrastructure gap faces the world, which further sustains both suboptimal antimicrobial stewardship and provokes higher levels of treatment failure and the development of additional antimicrobial resistance (Ture et al., 2025). The existence of these constraints indicates that there is an urgent need for scalable and cost-effective solutions that would help democratize access to optimized antimicrobial stewardship, possibly with the help of simplified predictive models or point-of-care diagnostics. In addition to resource limitations, the other acute obstacle is the natural variability of patients, with their physiological conditions varying as well as comorbidities, which can also cause substantial changes in drug disposition (Holmes et al., 2015). This inconsistency requires extremely personalized dosing schedules to reach treatment goals and reduce side effects, especially in drug-resistant infections, in which optimal exposure is the key to success (Bulman et al., 2022). This explains why ongoing studies on population-specific pharmacokinetic parameters and adaptive dosing algorithms are required to enhance treatment outcomes in patients from various population groups.
The development of more elaborate antimicrobial stewardship measures, including precision dosing by the model, requires strong interdisciplinary relationships between physicians, pharmacists, nurses, and laboratory staff to guarantee seamless information exchange n and coordination in patient care (Abdulla et al., 2021). Such a joint method is essential to maximize therapeutic effects because it will help to

adjust dosages in time according to clinical response, drug levels, and changing pathogen susceptibility information, which is dynamic and may be difficult to analyze without a variety of backgrounds (Alkhiyami et al., 2024; Kuehl et al., 2019). Nevertheless, in a clinical setting where there are conflicting priorities and scarce resources to focus on antimicrobial stewardship, such coordination may prove difficult (Amadi et al., 2024). In addition, the lack of complete validation plans and an accepted template for the implementation of emerging strategies, such as model-informed precision dosing, is a barrier to its successful introduction into clinical practice in the future (Abdulla et al., 2021).

Moreover, the emergence of antimicrobial resistance requires new ways of solving the problem other than traditional methods, especially since there are more cases of bacterial persistence and tolerance that cannot be identified by conventional detection methods and can lead to treatment failure (Gollan et al., 2019; Kuehl et al., 2019). The difference between resistance, tolerance, and persistence is important to inform treatment choices because persistent infections, which are defined by intermittent phenotypic resistance to deadly antibiotic levels, require different treatment options than genetically resistant infections (Fisher et al., 2017). This difference is instrumental in the process of maximizing antimicrobial therapy, as not only does suboptimal dosing, which is common in critically ill patients, undermines clinical outcomes and contributes to the development of antibiotic resistance (Yow et al., 2022). In turn, a more comprehensive insight into the mechanisms of such effects is essential to design more effective and sustainable antimicrobial regimens, especially in the context of broad inter-patient pharmacokinetic variability in the critical care environment (Cotta et al., 2023; Reza et al., 2024).

Conclusion

Optimization of antimicrobial treatment in intensive care patients, particularly those with multidrug-resistant infections is a complicated yet a vital provision in contemporary clinical practice. As noted in this review, the problem of antimicrobial resistance (AMR) is becoming increasingly severe, and the development of resistant pathogens has become an immediate global health issue. Critically ill patients have problems with optimal drug exposure, which is caused by their changed physiological conditions. The normal antimicrobial dosing procedures do not consider the large inter-patient pharmacokinetic differences that contribute to the possibility of under-therapeutic drug levels, as well as, drug toxicity. Individual dosage schedules and therapeutic drug monitoring (TDM) are part of clinical pharmacy interventions, which are important in reducing such risks. Clinical pharmacists can use personal pharmacokinetic/pharmacodynamics profiles to ensure that appropriate drug is given at the appropriate dose to avert treatment failure and resistance. In addition, the use of new pharmacokinetic tools, including Bayesian forecasting, in clinical practice can give a complex dosing method based on the individual patient and the resistance history of the pathogen. This is especially relevant in critical care units, where there is frequently a need to make fast changes to drug dosage. Nonetheless, even in the face of such difficulties as resource constraints and the necessity of specialized training, the implementation of these personalized approaches can contribute greatly to patient outcomes. In the future, the wider use of precision dosing initiatives and interdisciplinary efforts is necessary to improve the quality of antimicrobial therapy and fight against the increase in the threat of AMR.

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Author contributions

Although the initial author created the manuscript's original text, all writers made substantial contributions through data collecting and literature searches. Each author agreed to accept full responsibility for the work by taking part in the critical revision of the book and approving the final draft.

Conflict of Interest

Authors declare they don’t have any conflict of interest.

Ethical Approval

Not Applicable

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