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Pharmacotherapy Complexity In Severe Infectious Diseases: Clinical Pharmacy Strategies To Prevent Treatment Failure And Toxicity

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Abstract

Genital tuberculosis (GTB) is a common cause of infertility in resource limited and low- and middle-income countries and although traditionally only classically few presentations are taught in medical school, the fact that GTB is a differential of several conditions, confirms it is a rarely sung but important reminder. These pre-existing conditions can be complicated in their management by the profound pharmacokinetic and pharmacodynamic (PK/PD) alterations associated with critical illness, including capillary leak, fluid resuscitation, hypoalbuminemia, enhanced renal clearance and multi-organ dysfunction. The associated dynamic physiological alterations often make standard antimicrobial dosing regimens inappropriate, resulting in subtherapeutic exposure, treatment failure, resistance selection, or dose-dependent toxicity. At the same time, the increased minimum inhibitory concentrations, biofilm production and persister biofilm population further downgrade antimicrobial susceptibility, leading to persisting and recurrent infections. This review identifies multi-factorial determinants of pharmacotherapy complexity in severe infectious diseases and outlines how clinical pharmacy strategies are pivotal in reducing these pressures. Core interventions consist of individualized, PK/PD-guided dosing; therapeutic drug monitoring for narrow therapeutic index drugs; infusion optimization strategies; proactive toxicity monitoring; and pharmacist-led medication review, with the objective of reducing drug-related problems. Integrating clinical pharmacists as part of the multidisciplinary intensive care team and implementing clinical pharmacy services in an antimicrobial stewardship program (ASP) can reduce the number of prescribing errors, reduce adverse drug events, and reduce length of hospital stay and improve clinical outcomes. Newer methods such as model-informed precision dosing, biomarker-guided therapy, and artificial intelligence–informed clinical decision support provide exciting possibilities for even more individualized antimicrobial treatment. Together, pharmacy practice-based individualized pharmacotherapy directs drug exposure to a suitable quantity according to the specific biochemistry of the host, pathogen, and infection process to optimize therapeutic effectiveness while minimizing toxicity and resistance.

Keywords Antimicrobial resistance; Severe infections; Sepsis; Pharmacokinetics; Pharmacodynamics; Therapeutic drug monitoring; Clinical pharmacy; Antimicrobial stewardship; Drug toxicity; Precision dosing.

Introduction

Antimicrobial resistance is an escalating global threat to general health, and drug-resistant bacterial infections are estimated to result in the deaths of millions of people every year by 2050 (Ghanem, 2020). The development of new and re-emerging pathogens also contributes to this disturbing pattern, as well as the difficulties associated with the treatment of immunocompromised individuals and those with severe comorbidities (Santos et al., 2023). The inappropriate use of antimicrobials, including inappropriate selection, dosing, route, and duration, is another major cause of increasing resistance (AlShehail, 2025). The estimates of bacterial antimicrobial resistance morbidity and mortality showed that 4.95 million infections and 1.27 million deaths were caused by this phenomenon in 2019 alone, demonstrating the depth of the issue in global morbidity and mortality (Hommes & Surewaard, 2022). Such a crisis calls for the creation of a variety of therapeutic interventions, such as non-antibiotic antimicrobial agents and combinations, to increase the effectiveness of therapy and the number of surgical procedures necessary (Kadirvelu et al., 2024). Nevertheless, the dynamic nature of pharmacotherapy in serious infectious diseases, especially in critically ill patients, often results in suboptimal drug concentrations, which puts the patient at risk of treatment failure and toxicity (Huang et al., 2024; Kuehl et al., 2019). This is also aggravated by the fact that in critically ill patients, the pharmacokinetics are disturbed, and typical dosing regimens of multiple drugs will not achieve optimal drug exposure, which encourages both the occurrence of insufficient drug exposure and the possibility of adverse drug reactions (Huang et al., 2024).

In addition to antibiotic resistance, other issues, such as bacterial persistence in sheltered niches, such as biofilms, and inadequate pharmacokinetics in foci of infection, cause significant treatment failures and relapses (Gollan et al., 2019). To overcome these complex issues, novel antibiotic-sparing methods, such as bacteriophages and monoclonal antibodies, are essential for the specific lysis of pathogens and biofilm disruption, especially when conventional antibiotics fail to work with multidrug-resistant organisms (Geng et al., 2025). In addition, the ever-growing crisis of antimicrobial resistance, triggered by excessive use and incorrect prescriptions of antibiotics, requires a paradigm shift in antimicrobial stewardship to maintain the activity of last-resort antimicrobials and eliminate the spread of multidrug-resistant pathogens (Elshobary et al., 2025; Miteu et al., 2023; Puri et al., 2024). In particular, the excessive use of antibiotics in human and animal medicine, and in the latter case as growth factors in animals, has also played a supportive role in the emergence of antibiotic resistance due to genetic modification (Sen et al., 2023).

Such selective pressure enhances the development of antibiotic-resistant bacteria and creates an urgent demand to develop innovative clinical pharmacy, which would help maximize the benefits of antibiotics and reduce their negative effects (Chen et al., 2025; Olatunji et al., 2024; Yow et al., 2022). Even the scientific and technological progress fails to prevent the deaths of millions of people who succumb to infections every year, and more than 4 million deaths were caused by the development of pan-drug-resistant microorganisms in 2019 (Cesaro et al., 2025). These dark figures also highlight the need for more clinical pharmacy interventions to maximize antimicrobial regimens to tackle these emerging threats (Maji et al., 2019). The application of pharmacokinetic/pharmacodynamic (PK/PD) principles to individualize the pharmacodoses of antibiotics to maximize toxicity and minimize the risks of toxicity and the development of additional resistance is an essential strategy (Onita et al., 2025). This personalized treatment, typically with the help of therapeutic drug monitoring, is applied to maintain the most effective levels of antibiotics in the area of infection and resist the mechanisms of bacterial resistance with minimal systemic toxicity, especially in at-risk groups (Pea, 2022). Moreover, the primary role of antimicrobial stewardship programs is to reduce resistance by fostering the wise use of antibiotics through evidence-based recommendations and constant monitoring (Jagadeesan et al., 2025; Natanzi et al., 2025).

Characteristics of Severe Infectious Diseases

There are characteristic signs of severe infectious diseases, such as sepsis, septic shock, severe pneumonia, and complicated intra-abdominal infections, which require aggressive and precisely

targeted pharmacotherapeutic support (Mensa et al., 2021). They are typified by the rapid deterioration of physiological conditions, dysfunction of the organism, and an increased likelihood of mortality, which requires immediate and proper antimicrobial treatment in conjunction with strong supportive care (Song et al., 2021). The multifaceted interaction between pathogen virulence, host immune response, and different pharmacokinetic profiles in patients in a critical care unit serves as a prerequisite for the need to implement individualized treatment plans (Niu et al., 2024).

Antimicrobial resistance is a worldwide issue that complicates the treatment of these serious infections and results in approximately 700,000 deaths annually, further complicated by the indiscriminate use of antibiotics and insufficient development of new agents (Zhang et al., 2019). This alarming statistic substantiates the urgency of pursuing sophisticated clinical pharmacy programs to maximize the use of antibiotics and reduce the spread of multidrug-resistant pathogens (Elshenawy et al., 2025; Schellack et al., 2018). Sepsis has a high mortality rate (26.7 and may rise to 36.5 in patients with septic shock and abdominal sepsis); therefore, there is a significant need to provide effective antimicrobial treatment as quickly as possible (Song et al., 2021; Wang et al., 2024). Here, the erratic changes in the pharmacokinetics of the critically ill, including the increase in the volume of distribution and clearance by the kidneys, have a drastic effect on the effects of antibiotics, and unique dosing approaches are necessary to achieve optimal pharmacokinetic/pharmacodynamic outcomes (Gatti et al., 2021; Ha et al., 2017).

This personalized care is essential for enhancing patient survival in sepsis, a major cause of critical conditions and death worldwide (Hites, 2021). Severe infections, such as those caused by methicillin-resistant Staphylococcus aureus (S. aureus), which may result in bloodstream infections and deep-seated foci, may also lead to a mortality rate of up to 40 percent because of effective management necessitating a period of antimicrobial therapy and source control, even though success is low (Peck et al., 2019). These high mortality rates highlight the necessity of optimizing antibiotic dosing methods, such as teicoplanin, a glycopeptide commonly used to treat MRSA, particularly because of the high prevalence of the major cause of sepsis and other severe infections, *S. aureus* (Chen et al., 2023; Howden et al., 2023; Surewaard et al., 2016).

Pathophysiological alterations caused by drugs.

Critically ill patients are often characterized by major physiological imbalances that would fundamentally change the pharmacodynamics and pharmacokinetics of drugs, making it difficult to administer effective antimicrobial treatment (Pagani et al., 2011). These changes involve alterations in fluid balance, hyperdynamic circulation, and organ dysfunction, which may radically affect the distribution, metabolism, and excretion of antibiotics (Roggeveen et al., 2022). For example, higher levels of capillary permeability and fluid resuscitation in sepsis may increase the volume of distribution of hydrophilic antibiotics, resulting in subtherapeutic concentrations at the infection site (Bhandari et al., 2023). Hypoalbuminemia, prevalent in severe sepsis, may reduce the binding of some drugs to proteins, resulting in a portion of free, active drugs and the possibility of toxicity or a changed distribution process (Chen et al., 2023). Moreover, critical illness often alters drug clearance processes, enhancing or reducing renal and hepatic excretion, which complicates the correct choice of drug dose (Povoa et al., 2021; Tanaka, 2025). Such alterations in the body require an individual approach to the administration of antimicrobials, which should consider not only the specifics of the patient but also the organism causing the disease, the localization of the infection, and the pharmacokinetic and pharmacodynamic characteristics of the drug (Bhandari et al., 2023).

In particular, the changes in the pathophysiology of sepsis, such as high volumes of distribution and enhanced clearance, may result in underdose of antibiotics when standard dosage is used, thus unable to reach therapeutic goals and, instead, contribute to the development of resistance (Coopersmith et al., 2018; Shah et al., 2015). Additionally, the administration of antimicrobials among critically ill patients is a frequent problem, often resulting in mistakes, especially in cases involving pathogens with a high minimum inhibitory concentration (Lam et al., 2017; Povoa et al., 2021). This underscores the urgent requirement of therapeutic drug monitoring and dynamic dose modifications to achieve optimal drug exposure and clinical response in this susceptible patient group, especially in managing severe infections by resistant organisms such as methicillin-resistant Staphylococcus aureus (Liu et al., 2011). Patients frequently require enhanced pharmacological treatment, which is complicated by the increased rate of nephrotoxic drug consumption and combined antibiotic programs (Aroca-Martíne et al., 2022).

The subjected pharmacokinetic changes, which are usually precipitated by changes in cardiac output, tissue perfusion, end-organ dysfunction, capillary leakage, and hypoalbuminemia in critically ill patients, tend to lead to suboptimal exposure to drugs and eventual treatment failure (Felton et al., 2014).

Table 1. Determinants of Pharmacotherapy Complexity in Severe Infectious Diseases.

Determinant	Pathophysiological Basis	PK/PD Impact	Clinical Consequences	Pharmacy-Focused Mitigation
Organ dysfunction (renal/hepatic)	AKI, hepatic hypoperfusion, cholestasis	Reduced or unpredictable clearance; metabolite accumulation	Nephrotoxicity, hepatotoxicity, treatment interruption	Renal/hepatic dose adjustment, frequent reassessment, TDM for narrow-index drugs
Hypoalbuminemia	Inflammation, capillary leak, malnutrition	↑ Unbound drug fraction; altered Vd	Toxicity despite "normal" total levels	Interpret free concentrations, adjust targets, consider alternative agents
Fluid shifts & capillary leak	Sepsis, aggressive resuscitation	↑ Volume of distribution (hydrophilic drugs)	Subtherapeutic exposure early in therapy	Loading doses, extended/continuous infusions
Augmented renal clearance (ARC)	Hyperdynamic circulation (younger/septic patients)	↑ Drug elimination	Treatment failure, resistance selection	Higher doses, shorter intervals, early TDM
Altered PK/PD in critical illness	Variable perfusion, ECMO/CRRT	Failure to reach PD targets	Prolonged infection, mortality	Model-informed precision dosing
Biofilms & persister cells	Dormant phenotypes, protected niches	Reduced antibiotic killing	Relapse, chronic infection	Combination therapy, antibiofilm strategies
Polypharmacy	Multiple antimicrobials, ICU drugs	Drug–drug interactions	Toxicity, prescribing errors	Medication reconciliation, interaction screening

Factors Contributing to Pharmacotherapy Complexity

Organ dysfunction

Organ system dysfunction, one of the traits of critical illness, greatly changes the pharmacokinetic properties of drugs, resulting in unstable antimicrobial levels and an increased likelihood of clinical failure, antimicrobial resistance, or drug toxicity (Roberts et al., 2014). Renal drug clearance is reduced in acute kidney injury, which is common in most critically ill patients; thus, drug doses should be adjusted carefully to avoid accumulation and subsequent nephrotoxicity, particularly for those drugs with a narrow therapeutic index (Elias Pinheiro et al., 2019). Hepatic impairment, which is also prevalent in the population, can decrease the rate of drug metabolism, exposing the parent compounds and active metabolites to increased drug exposure (Cortegiani et al., 2023).

This modified physiology requires careful drug use and dose customization of antimicrobials, particularly to consider the impaired metabolic ability and avoid adverse drug reactions (Sulaiman et al., 2022). Moreover, because serum creatinine and estimated glomerular filtration rate (eGFR) may not be reliable measures of kidney performance in the fragile metabolic conditions of acute kidney disease, more specific drugs of kidney-cleared antibiotics may be more justified to drive dosage modifications (Pampa-Saico et al., 2020). Directly measuring drug concentrations, including colistimethate sodium, is important in unstable conditions to assess the correct dose, reduce drug resistance, and decrease the incidence of acute kidney injury (Pampa-Saico et al., 2020).

Hypoalbuminemia, which results in increased antibiotic-free fractions, higher volume of distribution, and hepatic or renal dysfunction, is one of the major changes in drug pharmacokinetics commonly observed in critically ill patients, and it impairs renal clearance (Ramos et al., 2023). The combination of these pathophysiological alterations, including renal failure, augmented renal clearance, impaired hepatic function, altered fluid status, and changes in serum albumin concentrations, often results in suboptimal drug concentrations or excessive levels, and subsequently, the risk of treatment failure, antimicrobial resistance, or toxicity becomes more probable (Drager et al., 2024; Tanaka, 2025). This type of complicated pharmacokinetic change in critically ill patients can commonly lead to a situation in which therapeutic drug monitoring is necessary to provide ideal drug exposure and clinical efficacy, particularly for drugs with a narrow therapeutic index (Ramos et al., 2023). Such a personalized approach is further complicated by the dynamicity of critical illness, when the clinical state of a patient may change considerably over time and require constant re-evaluation and readjustment of medications (Povoa et al., 2021).

Altered PK/PD

PK/PD changes in critically ill patients, including changes in drug clearance and apparent volume of distribution, often result in a lack of adequate antibiotic concentrations in areas of infection, contributing to an increase in the duration of stay and unfavorable outcomes (Liang et al., 2023). The main cause of this phenomenon is the high level of pharmacokinetic variability, and successful changes in the optimal dose of antibiotics are difficult to predict (Roberts et al., 2019). For example, polymyxins have complicated pharmacokinetics in critically ill patients, which are sensitive to renal function, body weight, and acute kidney injury, and require individualized dosages to produce therapeutic effects and reduce toxicity (Zamri et al., 2025). In particular, increased renal clearance and a large volume of distribution, which are common features among critically ill patients, require higher and more frequent dosing of antibiotics to achieve therapeutic levels (Fawaz et al., 2020).

Table 2. Clinical Pharmacy Strategies to Prevent Treatment Failure and Toxicity.

Strategy	Core Tools	Clinical Application	Primary Benefit	Outcome Metrics
Individualized dosing	PK/PD indices (AUC/MIC, fT>MIC)	Sepsis, septic shock, MDRO infections	Optimized pathogen killing	Target attainment rates
Therapeutic drug monitoring (TDM)	Serum concentrations, Bayesian models	Vancomycin, aminoglycosides, polymyxins	Reduced nephro/neurotoxicity	AKI incidence, dose accuracy
Infusion optimization	Extended/continuous infusion	β-lactams, vancomycin	Improved tissue exposure	Time to clinical response
Medication review	Pharmacist-led reconciliation	ICU polypharmacy	↓ Prescribing errors	DRP reduction (major/minor)
Toxicity surveillance	Renal/hepatic labs, neuro checks	High-risk antimicrobials	Early harm detection	ADE rates
Stewardship interventions	De-escalation, duration control	Empiric → targeted therapy	Resistance mitigation	Antibiotic days, LOS
Multidisciplinary ICU rounds	Real-time dose adaptation	Dynamic critical illness	Faster decision-making	Mortality, ICU LOS
AI/decision support (emerging)	ML models, CDSS	Precision dosing prediction	Scalable personalization	Predictive accuracy

To add to this complexity, hypoalbuminemia is common among critically ill children, and it elevates the unbound fraction of highly protein-bound drugs, thereby affecting their dispersion to peripheral tissues (Hartman et al., 2019). In addition, paradoxically, augmented renal clearance, which is an acceleration in the glomerular filtration rate, is also noted in a large proportion of adult and pediatric patients with critical illness, which further complicates the administration of antibiotics by increasing the rate of drug excretion and, therefore, possibly resulting in subtherapeutic levels (Hartman et al., 2019; Thakkar et al., 2017). This increased clearance may render conventional antibiotic regimens ineffective, particularly those with time-dependent properties. Therefore, it is necessary to optimize dose measurements and therapeutic pharmacodynamics to achieve appropriate pharmacodynamic outcomes (Povoa et al., 2021; Williams et al., 2023).

These issues are especially acute with antibiotics such as quinolones, beta-lactams, glycopeptides, and linezolid, since specific pharmacodynamics/pharmacokinetics equations are associated with better clinical recovery and a lower death toll in retrospective studies (Roberts et al., 2014). Such a complicated interplay highlights the importance of individual dosing plans for antibiotics in critically ill patients, using real-time physiological variations and drug-individual pharmacokinetic rates to optimize the results (Bhandari et al., 2023). This complex interaction between the pathophysiology of the host and the pharmacokinetics of drugs underscores the need to improve dose adjustments to adequately expose the drug, which may include increased drug dose, increased frequency of drug doses, or even longer infusion in critically ill children (Schouwenburg et al., 2021). This necessitates the introduction of model-based precision dosing plans, particularly for beta-lactam antibiotics, to account for the significant pharmacokinetic heterogeneity of the population at risk and to prevent therapeutic failure (Gijsen et al., 2021; Girdwood et al., 2022).

Combination antimicrobial therapy

In addition to the use of single-agent regimens to optimize them, combination antimicrobial therapy is often used in severe infectious disease cases, especially polymicrobial infections, or to expand empirical coverage against resistant pathogens. This is expected to promote synergistic effects, reduce the development of resistance, and improve the bactericidal effect, but may result in an increased probability of drug-drug interactions and complexity of treatment (Zelmer et al., 2022). For example, the Yin-Yang model recommends that combination therapy addressing both growing and non-growing persister cells is essential to eliminate persistent infections, which, in turn, is successful with the help of drugs such as pyrazinamide, daptomycin, and colistin (Niu et al., 2024).

Likewise, anidulafungin with colistin or gentamicin has been shown to be effective in eliminating pre-existing biofilms of Pseudomonas aeruginosa, indicating the possibility of such combinatorial strategies against resistant microbial structures (Ghanem, 2020). Moreover, it has been reported that the combination of agents with dissimilar antimicrobial effects, such as silver and tobramycin, can increase their effect and avoid microbial resistance in diseases of biofilms (Francolini & Donelli, 2010). Such a synergistic combination, used with agents that have different mechanisms of action, is especially useful in dealing with the complicated issues of biofilms that are notoriously difficult to target using single-target therapies (Abdelhamid & Yousef, 2023). Additionally, the choice of a combination of different drugs is important, as the interaction of some antibiotics can be antagonistic or stimulate the development of tolerance; therefore, drug interactions and resistance profiles must be carefully considered (Niu et al., 2024). The co-administration of combinations such as colistin-tobramycin has been proven to be much more effective against P. aeruginosa infection than either of the two antibiotics, showing a high level of reduction in bacterial cells both in vitro and in vivo (Ghanem, 2020).

Risks of Treatment Failure and Toxicity

However, subtherapeutic exposures caused by modified pharmacokinetics, commonly found in critical illness, contribute to ineffective pathogen eradication, especially biofilm-associated pathogens, which increases the risk of persistent infection and treatment failure (Badawy et al., 2023). In addition, the existence of persister cells and biofilms that are naturally more resistant to traditional antimicrobial agents makes it necessary to use innovative strategies that specifically target these antibacterial bioburdened forms (Francolini & Donelli,2010; Niu et al.,2024; Niu et al., 2024). While the induction of these persister cells has been largely characterized by environmental stresses, such as antibiotics, temperature, pH, and nutrient starvation in vitro, host stimuli during growth in vivo, including the

uptake of bacteria by macrophages, are also incorporated into this regulatory framework (Niu et al., 2024).

Second, the rapid development of antibiotic resistance through selection pressure due to suboptimal drug concentrations may lead to treatment failure, often requiring higher toxicity last-line antibiotics. This requires nuanced antibiotic stewardship that ensures the cure of the pathogen while minimizing collateral damage and preventing the emergence of resistance. The toxicity of many highly effective antimicrobial drugs exacerbates these challenges, as they can cause serious adverse drug reactions, organ injury from aggressive therapies, and prolonged hospitalizations. Nephrotoxicity associated with colistin and aminoglycosides, for example, requires close renal function and therapeutic drug monitoring to prevent sustained patient harm from toxicity while maintaining the therapeutic effect (Niu et al., 2024).

Table 3. High-Risk Antimicrobials in Critical Care: PK/PD Targets and Safety Considerations.

Drug / Class	Primary PK/PD Target	Common ICU PK Challenges	Key Toxicities	Optimization Approach
Vancomycin	AUC/MIC 400–600	Variable clearance, poor tissue penetration	Nephrotoxicity	Bayesian AUC-guided dosing, CI
Aminoglycosides	Cmax/MIC ≥8–10	ARC, altered Vd	Nephro- & ototoxicity	Once-daily dosing, TDM
β-lactams	fT>MIC (100% in severe infection)	ARC, ECMO/CRRT losses	Neurotoxicity (high levels)	Extended/continuous infusion
Polymyxins (colistin)	AUC/MIC (exposure-limited)	Complex renal handling	Severe nephrotoxicity	Individualized dosing, strict monitoring
Linezolid	AUC/MIC, trough 2–8 mg/L	Myelosuppression risk	Thrombocytopenia	TDM, duration limitation
Combination regimens	Synergistic PD targets	Interaction complexity	Additive toxicity	Pharmacist-guided selection

Drug accumulation and adverse effects

However, in critically ill patients, the risk of toxicity is increased by the unstable nature of their physiology, making them more sensitive to adverse effects due to the same accumulation of drugs, albeit within the therapeutic range. This accumulation may occur as a result of decreased renal or hepatic clearance and altered protein binding and distribution volume, which may increase drug levels and eventually cause more adverse drug reactions (Ramos et al., 2017; Timsit et al., 2017). Therefore, therapeutic drug monitoring is important in this population to achieve optimal drug exposure with minimal risk of dose-dependent toxicities. A major challenge is the rise of antibiotic resistance, which can enable bacteria to proliferate in the presence of drugs, whereas antibiotic tolerance can allow bacteria to survive multiple antibiotics for prolonged periods and increase the odds of developing resistance (Arulkumaran et al., 2020; Lu et al., 2025). This difference is crucial for understanding treatment failures, as tolerant bacteria are not resistant in the classical sense but can endure antibiotic stress and remain infectious, resulting in persistent infections and an increased risk of relapse (Fisher et al., 2017; Kühl et al., 2019). In addition, the major modifications in the physiology of critically ill patients [1], such as increased renal clearance, could cause subtherapeutic concentrations of antibiotics that can lead to treatment failure and resistance, making personalized antibiotic dosing strategies mandatory (Pea, 2022).

These discrepancies in methodology would explain the clinical need for a validated tool to characterize and quantify antibiotic tolerance and persistence and the lack of standardized measurements in the literature, as the correlation between different measures within/among patient populations is often inconsistent (Kühl et al., 2019). While the clinical significance of antibiotic tolerance and persistence has been well established (Kühl et al., 2019), no new classifiers or quantifiable cut-offs have been

implemented that might apply directly to the clinic. However, much work remains to be done to develop these parameters into clinically useful tools that could more effectively inform antimicrobial therapy through the consistent, standardized application of appropriate metrics relevant to these phenomena. This interplay of pharmacokinetics, pharmacodynamics, and microbial resistance mechanisms presents challenges in the context of severe infectious diseases that can best be addressed with precision medicine approaches to predict optimal patient outcomes. As a matter of fact, influenced by drug metabolism and clearance variability, as well as by these dynamic physiological changes accompanying critical disease, personalized antibiotic regimens and real-time drug-level monitoring are typically required to ensure (blank) optimal therapeutic exposure (Vincent et al. 2019).

Clinical Pharmacy Strategies

Individualized dosing, particularly in the context of critically ill patients, personalized antimicrobial therapy, adaptation of the antibiotic pattern, and dosages to individual patient characteristics and dynamics of infection are important for ensuring optimal drug effectiveness and safety (Moser et al., 2019; Pea, 2022). This method is especially important when dealing with critically ill patients, whose pharmacokinetics are often unpredictable, making conventional dosing regimens likely to yield suboptimal drug concentrations (Corona et al., 2023). This variability can be countered with an effective strategy: therapeutic drug monitoring, which allows for adequate exposure to the antibiotic and low toxicity (with the exception of some antibiotics, such as vancomycin, aminoglycosides, and beta-lactams) (Ramos et al., 2023; Tanaka, 2025). This approach, when combined with the principles of pharmacokinetics/pharmacodynamics (PK/PD), enables actual dose adjustments tailored to individual patient characteristics, pathogen type and susceptibility, and site of infection, as opposed to adhering to standard fixed-dose regimens (Yow et al., 2022). In addition, more sophisticated antibiotic-pathogen-host interaction models enable the prediction of treatment success, providing the basis for a precision medicine approach (Bulman et al., 2022). However, pharmacokinetic/pharmacodynamic modeling combined with machine learning algorithms can provide an even more sophisticated basis for targeting individualized dosing, which can lead to predictive analytics of optimal antimicrobial selection and resistance mitigation in critically ill patients (Huan et al., 2025).

Monitoring biomarkers and drug levels

Numerous recommendations now advocate for real-time antibiotic exposure optimization in critically ill patients to reach and maintain optimal antimicrobial PK/PD targets as soon as possible (Gatti et al., 2022). TB PD-TDM encompasses more than simply measuring drug concentrations, but doing so in the light of the dynamically changing condition of the patient, their pathogen susceptibility, and the respective pharmacodynamic targets of the specific antibiotic (Roberts et al., 2019). For example, in the context of serious infections, a common practice target is to keep vancomycin trough concentrations above 15 μg/mL to optimize both the risk of penetration into the site of infection and the emergence of resistant strains, although higher vancomycin trough still may not consistently improve outcomes86 (Liu et al., 2011).

Finally, traditional trough-based monitoring has been complemented with newer approaches, including model-informed precision dosing, to address the important shortcomings of the trough-based approach and provide more dynamic and patient-specific vancomycin dosing (Geng et al., 2025; Roggeveen et al., 2019). Studies have shown that for vancomycin efficacy, an AUC/MIC ratio greater than 400 is essential (especially for MICs MIC), which is an important pharmacodynamic target for beta-lactams against susceptible organisms (Roberts et al., 2014). In addition, sophisticated analytical methods, possibly utilizing artificial intelligence and machine learning, may aggregate real-time patient data and provide predictions for incorrect dosing regimens, modifying for changing pathophysiology and pathogen susceptibility (Singh et al., 2024).

Early detection of toxicity

Vigilance in monitoring adverse drug reactions and nephrotoxicity, particularly with renally cleared antibiotics, is key to preventing irreversible organ damage in patients with severe infections (Liu et al., 2011). It is essential to possess a thorough knowledge of the toxicities associated with individual drugs and implement preventive measures in an anticipatory manner (i.e., dose modifications based on renal function and cautious co-administration of nephrotoxins) (Liu et al., 2011). Because renal impairment

is common in critically ill populations, it is important to consider dose regimens associated with less nephrotoxicity (Lizza et al., 2022). For example, it has been shown that the risk of nephrotoxicity is lower with continuous infusion than with intermittent dosing of vancomycin.
In addition, the concomitant use of more than one nephrotoxic agent, such as aminoglycosides and vancomycin, increases the risk of developing renal injury and requires closer monitoring (Liu et al., 2011). This requires the use of clinical decision support systems and multidisciplinary team strategies to detect high-risk patients and deliver timely interventions to prevent the development of renal toxicity. In addition to direct directly causing kidney damage, more systemic toxicities must be carefully taken into account as well (such as neurotoxicity and ototoxicity, two late toxicity that could occur insidiously and affect patient's quality of life). This is associated with a specific risk necessitating an active pharmacovigilance plan of regular clinical evaluation and laboratory biomarkers to identify and manage late-onset toxicities. Nevertheless, few data have been reported and focused on beta-lactam antibiotic toxicity and the best ways to capture that toxicity, pointing to an important gap in the current pharmacovigilance infrastructure (Antimicrobial Therapy in Intensive Care Unit, 2023).

Interdisciplinary Collaboration

Role of clinical pharmacists in ICU teams

Their knowledge of pharmacokinetics, pharmacodynamics, and drug interactions allows them to optimize antibiotic regimens and limit adverse effects in such complex patient populations. For patients receiving continuous renal replacement therapy, sustained low-efficiency dialysis, or extracorporeal membrane oxygenation, clinical pharmacists play a key role in personalizing dosing strategies to optimize antimicrobial exposure, which may be disrupted by the underlying altered clearance driving mechanisms (Liang and Kumar, 2015). They also play an important role in preventing drug-drug interactions and dose-dependent toxicities, such as nephrotoxicity from aminoglycosides or vancomycin and neurotoxicity from beta-lactams, thus protecting organ function in critically ill patients (Arulkumaran et al., 2020; Fiore et al., 2021; Maji et al., 2019).
This active engagement involves significant participation in antimicrobial stewardship programs, guideline development, formulary management, and prospective audits and feedback to optimize antibiotic use and combat resistance (Eid et al., 2022; Singh et al., 2017). Medication errors are more frequent in the intensive care unit owing to high care complexity and polypharmacy (Nascimento et al., 2023). Hence, clinical pharmacists also play an important role in ensuring patient safety by identifying and resolving medication errors. Additionally, their active participation in multidisciplinary rounds enables the integration of complex pharmacotherapy data and adjustment of treatment regimens to optimize patient outcomes (Gatti & Pea, 2021; Krishna, 2021).
Such expertise is especially important in critically ill patients, where altered pharmacokinetics and pharmacodynamics require customized dosing and careful adjustment to avoid underdosing and treatment failure on the one hand (Khilnani et al., 2024; Williams et al., 2023) and overdosing and toxicity. For example, 10–15% of ICU patients on beta-lactam antibiotics experience neurotoxicity; therefore, very little direct toxicity data exist, but monitoring must be vigilant ("Antimicrobial Therapy in Intensive Care Unit," 2023). It has been established that their incorporation into the critical care team decreases adverse drug reactions, increases medication safety, and reduces pharmaceutical costs through appropriate drug selection and dosing (Agarwal, 2021; Ismail & Alharbi, 2024).

Evidence Supporting Clinical Pharmacy Involvement

Outcome improvement data

Multiple studies show that clinical pharmacist interventions can lead to significant improvements in patient outcomes in the critical care setting, with preventable adverse drug events reduced by 66–70% and decreased length of stay (Lee & Gettman, 2018; Wei et al., 2024). There have been significant improvements in drug-related issues, with a 63% decrease in total and a major (85%) decrease in major DRPs after pharmacist-conducted medication reviews [18]. In addition, because they prevent adverse events and monitor individual patients, the cost avoidance associated with their skills offers a significant return on investment (Kane-Gill et al., 2003). Aside from direct costs, their existence within the ICU

has also been associated with a better chance of survival and a decreased risk of postoperative mortality (Radhakrishna & Ravindran, 2022).

Such advancements in patient care have contributed to increased survival rates among patients, both those enrolled in clinical trials and those treated in hospitals involved in other research (Radhakrishna & Ravindran, 2022). Clinical pharmacists are also directly involved in critical care units, and there is evidence that their involvement decreases medication errors, which are common in high-complexity environments where more than 20 high-risk medications may be administered daily (Kessemeier et al., 2019; Sikora & Martin, 2022). Clinical pharmacists have played a crucial role in decreasing healthcare-associated infections by utilizing specialized interventions and monitoring, such as catheter-associated urinary tract infections (Sharma et al., 2023). Similarly, life-saving benefits of decreased mortality and length of stay have been demonstrated with the inclusion of critical care pharmacists in multidisciplinary teams (Wei et al., 2024).

Such improvements are attributed to their engagement in optimizing drug therapy, such as drug indication, duplication, and inappropriate prescribing (Althomali et al., 2022). Their participation has been associated with a decrease in prescribing errors by 66 percent, highlighting their importance in patient safety in ICUs (Ismail & Alharbi, 2024). Moreover, a systematic review and meta-analysis demonstrated that pharmacists as part of multidisciplinary teams significantly improved patient outcomes, with decreased mortality, reduced ICU length of stay, and decreased adverse drug events (Chiang et al., 2020). The main impact of this multidisciplinary approach (particularly pharmacist-led interventions) was well demonstrated, as it provided 84.8% of major DRP combat and significant improvement of moderate DRP via optimization of antimicrobial dosing and administration protocols (Aksoy et al., 2025).

Future Approaches

Advanced monitoring tools

Artificial intelligence and machine learning algorithms have the potential to transform adverse drug event monitoring, moving beyond traditional pharmacokinetic metrics to monitor real-time physiological data and susceptibility based on genetic backgrounds. Next-generation devices may predict drug-drug interactions and patient-specific responses more accurately, further reducing the risk of complex pharmacotherapy before unwanted outcomes occur (Singh et al., 2024).

This will allow for unprecedented opportunities for the enhancement of medication safety from pharmacists, as these technologies will be able to provide continuous performance monitoring and early detection of adverse drug reactions, rather than using traditional methods, which are largely retrospective (Noorain et al., 2023; Wei et al., 2024). Additionally, AI-based models can predict drug responses and key pharmacokinetic parameters in the organismal environment, facilitating an optimal dosing regimen and limiting the reliance on vast and expensive in vitro and in vivo assays (Noorain et al., 2023). AI has the potential to analyze large sets of patient data for optimal drug formulations and accelerate clinical trial development, making drug development more efficient (Ali et al., 2024).

AI-driven clinical decision support systems in the intensive care unit have the potential to progress from basic rule-based systems to more sophisticated ones (Liu et al., 2015) and provide expert-level, individualized care by integrating multiple medication-related data inputs. This will allow for the real-time, accurate tailoring of drug regimens, especially in multiple organ dysfunction scenarios, where traditional methods are often inadequate given the variability in drug clearance and distribution (Meng et al., 2025; Wei et al., 2024). Artificial intelligence and machine learning models have enabled the discovery of complex relationships between multiple physiological features, drug properties, and patient-specific characteristics, facilitating accurate and individualized therapy (Noorain et al., 2023).

Personalized pharmacotherapy models

Powered by advances in Artificial Intelligence and Machine Learning, these models move beyond the one-size-fits-all standard of patient care and utilize an individualized profile of a patient's unique biological and pharmacological profiles to maximize drug selection and dosing (Sikora et al., 2023). AI algorithms can analyze large datasets that include genetics, physiology, and the response of a patient to medications to accurately guide individualized pharmacokinetics and pharmacodynamics, allowing for tailoring for improved outcomes (Pawar et al., 2023). Such hierarchical degrees of personalization

are critical in acute infectious diseases, where inter-patient variations in drug metabolism and response significantly affect both target efficacy and organ toxicity levels (Dey et al., 2024). Moreover, artificial intelligence methods are skilled at detecting multisectoral associations among many variables encompassing sex, genotype, lifestyle choices, and environmental influences that commonly interact to produce complex diseases and need to be considered when integrating diverse datasets (Noorain et al., 2023).

AI has immense potential in personalizing medicine, particularly for applications in genetic-based tailoring of therapeutic strategies by calculating how individual patients respond to specific treatments, thereby increasing therapeutic efficacy while reducing adverse effects (Singh et al., 2024). In addition, AI-based tools can predict the future demand for any pharmaceutical product, facilitate inventory management, and optimize supply for on-time delivery and patient accessibility.

Deep learning algorithms can explore enormous biological and chemical databases on a vast scale to predict therapeutic effectiveness and toxicity, improve drug candidate selection, and enhance the drug development process (Pawar et al., 2023). While AI already bolsters model performance by encapsulating heterogeneity present in-patient features, the integration of these into predictive models remains an ongoing challenge to strengthen predictive capabilities in pharmacodynamic modeling and simulation (Pawar et al., 2023). This new generation of models goes beyond increasing patient stratification in clinical trials to predicting adverse events based on genomics and treatment history, allowing risk mitigation before they occur and safer drugs (Dangeti et al., 2023). AI has the potential to accelerate the pace of personalized medicine by enabling extensive genomic and clinical data analysis to determine novel biomarkers and predict responses to drugs at the patient-specific level (Uppalapati et al., 2024).

Conclusion

Pharmacotherapy in severe infectious diseases embodies a paradigm of one of the most complex areas of modern clinical practice, with rapid physiological deterioration, multidrug-resistant pathogens, and narrow therapeutic margins all converging to jeopardise the end result in the patient. Given the profound and rapid changes in drug disposition and pharmacokinetics/pharmacodynamics characteristics of critically ill patients, standardized antimicrobial dosing strategies are often inadequate and do not result in appropriate PK/PD target attainment. Too little exposure leads to both treatment failures and the development of resistant pathogens, while too much exposure increases the risk of nephrotoxic and neurotoxic damage and other important adverse drug events. The literature referenced illustrates that the risk discussed can be significantly reduced with deliberate, clinically pharmacy-driven interventions. Therapeutic drug monitoring and pharmacokinetic/pharmacodynamic modeling have opened the possibility of individualized dosing strategies, recommending adaptive adjustment of antimicrobial regimens to changing clinical states. The role of intensive care team–embedded pharmacists in medication optimization, toxicity, complex combination therapy management, and avoidance of medication errors Compelling data show that these interventions decrease drug-related problems, adverse events, length of stay, and healthcare costs, while improving survival. Further embedding model-informed precision dosing, artificial intelligence and machine-learning–based decision support systems will likely improve the level and degree of antimicrobial personalization, especially in highly complex pharmacotherapy environment. Nonetheless, realizing this promise requires cross-disciplinary work, the appropriate infrastructure, and constant education. Summary clinical pharmacy is an integral part of the management of severe infectious diseases, and thus, a key component of safe, effective, and sustainable antimicrobial therapy in the era of antimicrobial resistance.

Conflict of Interest

The authors declare they don’t have any conflict of interest.

Author contributions

The first author wrote the first draft of the paper, which was supervised by a cross-responding author. Each author contributed to the manuscript's writing, gathered information, edited it, made tables, and received approval to submit it to a journal for publication.

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