Natural Resources for Human Health
eISSN: 2583-1194

Review Article

Received: 25 January 2026
Revised: 26 February2026
Accepted: 27 March 2026

Natural Resources for Human Health 2026, Vol. 6 (2): 648-658

KEYWORDS:
Antibiotics; Pharmacokinetics; Pharmacodynamics; Minimum inhibitory concentration; Therapeutic drug monitoring; Antimicrobial stewardship; Precision dosing

Antibiotics Pharmacokinetics and Pharmacodynamics Narrative Review Study: Clinical Implications for Optimizing Therapy

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ABSTRACT: Antibiotic therapy is most effective when the administered regimen produces drug exposure sufficient to inhibit or eradicate the causative pathogen at the infection site while limiting toxicity and unnecessary selection pressure. Pharmacokinetics (PK) describes absorption, distribution, metabolism, and elimination, whereas pharmacodynamics (PD) characterizes the relationship between antimicrobial exposure and microbiological effect. Their integration provides a rational basis for dose, interval, infusion strategy, monitoring, and treatment duration. The principal PK/PD indices used in antibacterial therapy are the fraction of the dosing interval during which free concentrations exceed the minimum inhibitory concentration (fT>MIC), the ratio of peak concentration to MIC (Cmax/MIC), and the ratio of free 24-hour area under the concentration–time curve to MIC (fAUC24/MIC). These indices differ by drug class and cannot be treated as interchangeable. Clinical application is complicated by altered physiology in critical illness, renal dysfunction, obesity, burns, pregnancy, pediatrics, and extracorporeal support; variable tissue penetration; uncertainty in MIC measurement; and the gap between preclinical targets and bedside outcomes. Strategies such as loading doses, extended or continuous β-lactam infusion, aminoglycoside extended-interval dosing, vancomycin AUC-guided monitoring, therapeutic drug monitoring (TDM), and model-informed precision dosing can improve exposure attainment in selected settings. Optimization must also incorporate source control, microbiological reassessment, de-escalation, and evidence-based duration. This narrative study summarizes core antibiotic PK/PD concepts, class-specific principles, patient-level variability, monitoring approaches, and practical implications for antimicrobial stewardship. It emphasizes that targets are context-dependent and should be interpreted with clinical guidelines, susceptibility data, infection site, and individual safety factors.

Natural Resources for Human Health
eISSN: 2583-1194

1. INTRODUCTION

Antibiotics remain central to the management of bacterial infections, yet their effectiveness is constrained by increasing antimicrobial resistance, differences in pathogen susceptibility, and substantial variability in drug exposure among patients. A dose that is adequate for one patient may be ineffective or toxic in another, even when the same organism and infection syndrome are involved. The challenge is particularly apparent in severe infections, where physiological changes can rapidly alter drug disposition and the consequences of delayed or inadequate exposure are substantial [1,2,3]. The PK/PD approach links the concentration-time profile produced by a regimen to the antibacterial effect. PK quantifies what the body does to the drug, while PD describes what the drug does to the microorganism and, indirectly, the host. This relationship informs the selection of dose, frequency, infusion duration, and monitoring strategy.

It also provides a framework for understanding why some agents are best administered in frequent or prolonged infusions, whereas others benefit from high peak concentrations or total daily exposure [1,4]. PK/PD is not a stand-alone prescription algorithm. Clinical outcome is influenced by source control, immune status, infection burden, tissue penetration, organism virulence, susceptibility testing, and the quality of supportive care. The MIC is an in-vitro measure and does not fully capture bacterial population dynamics or the drug concentration at the infected site. Thus, PK/PD targets should be treated as useful exposure goals rather than guarantees of cure [4,5]. This study presents core PK and PD concepts and translates them into practical clinical considerations for common antibacterial classes, special populations, TDM, and antimicrobial stewardship.

2. FUNDAMENTAL PRINCIPLES OF ANTIBIOTIC PHARMACOKINETICS

2.1 Absorption and bioavailability

Absorption describes the movement of a drug from its administration site into systemic circulation. Intravenous administration provides complete systemic bioavailability and is often preferred when rapid, predictable exposure is required in severe infection. Oral bioavailability varies by antibiotic and can be affected by food, gastrointestinal motility, vomiting, malabsorption, chelation with polyvalent cations, and drug interactions. Agents with high oral bioavailability may permit an effective intravenous-to-oral switch once the patient is clinically stable, the infection site is appropriate, and an active oral option is available. The switch should be based on the total clinical picture rather than a fixed number of treatment days [5]. Oral step-down depends on the exposure achieved by the specific formulation, the organism's susceptibility, the infection site, and the patient's ability to absorb and take the drug reliably. Linezolid has near-complete oral bioavailability. Ciprofloxacin tablets provide approximately 70% absolute bioavailability, and coadministration with polyvalent cations can further reduce absorption. These differences illustrate why intravenous-to-oral conversion should follow drug-specific evidence [6,7].

2.2 Distribution and volume of distribution

Distribution is the movement of drug from plasma into tissues and body fluids. The apparent volume of distribution (Vd) relates the amount of drug in the body to its measured plasma concentration. Hydrophilic agents, including many β-lactams and aminoglycosides, distribute mainly within extracellular fluid; their Vd can increase with fluid resuscitation, edema, ascites, or capillary leak. Lipophilic agents generally penetrate intracellular compartments more extensively, although penetration is agent- and tissue-specific. Protein binding also affects free drug concentrations, which are particularly relevant to many PK/PD targets. Hypoalbuminemia can increase the unbound fraction of highly protein-bound drugs while also changing clearance and distribution; the net effect cannot be predicted from albumin alone [2,8].

2.3 Metabolism

Antibiotic metabolism may occur through hepatic enzymes, nonenzymatic pathways, or other tissues. Hepatic impairment, enzyme induction or inhibition, and interacting medications can change exposure for selected agents. The clinical impact varies by drug: some antibiotics rely predominantly on renal elimination, whereas others undergo substantial hepatic or biliary clearance. Drug-specific prescribing information and interaction resources remain essential, particularly for macrolides, rifamycins, and agents with clinically important CYP-mediated interactions [8].

2.4 Elimination, clearance, and half-life

Clearance is the volume of plasma from which drug is removed per unit time and is a major determinant of maintenance dosing. Renal elimination may involve glomerular filtration, tubular secretion, and reabsorption. Reduced kidney function can cause accumulation and toxicity, while augmented renal clearance (ARC), often observed in younger trauma or sepsis patients, may lead to underexposure. Half-life is influenced by clearance and Vd; it helps describe drug persistence but should not be used in isolation to set dosing intervals. Renal replacement therapy (RRT) introduces additional variables, including modality, effluent rate, filter characteristics, residual renal function, and timing of drug administration [2,8].

2.5 Loading and maintenance doses

A loading dose is intended to achieve a desired concentration promptly and is primarily related to Vd and the target concentration. It may be necessary when the Vd is expanded or when early exposure is important. A maintenance regimen

replaces drug eliminated over time and is primarily determined by clearance and the exposure goal. In practice, a loading dose may remain appropriate in renal dysfunction when rapid therapeutic exposure is required, while the maintenance dose or interval is subsequently adjusted to reflect elimination. The distinction is particularly relevant in sepsis, where fluid shifts can enlarge Vd at the same time that renal clearance is reduced or increased [8].

2.6 Infection-site penetration

Plasma concentrations do not necessarily represent exposure at the infection site. Penetration into cerebrospinal fluid, bone, epithelial lining fluid, abscesses, prostate, or intracellular compartments differs among drugs and may be altered by inflammation, perfusion, pH, and protein binding. An agent with favorable plasma PK/PD may be unsuitable when tissue penetration is inadequate. Abscess drainage, removal of infected devices, and other source-control measures can improve the likelihood of cure and reduce the need to compensate for an inaccessible infectious focus by escalating antimicrobial exposure [3,4].

Central nervous system infection illustrates the limits of using plasma exposure as a surrogate. Entry into cerebrospinal fluid depends on the properties of the drug and on the degree of meningeal inflammation. As inflammation resolves, penetration may change even if the plasma concentration is stable. Agent selection for these infections therefore requires evidence of adequate central nervous system exposure and activity against the causative organism [9].

3. PHARMACODYNAMIC MECHANISMS AND INDICES

3.1 MIC and susceptibility interpretation

The minimum inhibitory concentration (MIC) is the lowest tested concentration that prevents visible growth under standardized laboratory conditions. MIC values support susceptibility categorization when interpreted against organism- and drug-specific breakpoints. They are affected by testing method, inoculum, growth conditions, and measurement variability, commonly around one dilution. The MIC is therefore a useful but imperfect representation of pathogen susceptibility. A breakpoint is not itself a universal therapeutic target; it incorporates microbiological, PK/PD, and clinical evidence. Clinicians should interpret reported susceptibility in the context of infection site, regimen feasibility, and the applicable laboratory standard [5,10]. Susceptibility reporting should identify the breakpoint system used. In the EUCAST system, “I” means susceptible with increased exposure, which can be achieved through an appropriate regimen or through drug concentrations at the infection site. CLSI and EUCAST categories should be interpreted against their respective organism–drug tables and dosing assumptions. A small difference between measured MICs can also reflect assay variability, especially close to a breakpoint [5,10,11].

3.2 Time-dependent activity: fT>MIC

For many β-lactams, antibacterial activity is most closely associated with the percentage of the dosing interval during which free drug concentration exceeds the MIC (fT>MIC). Increasing the dose may raise concentrations but, beyond a point, extending the duration above MIC through shorter intervals or prolonged infusion may be more efficient. The exposure target differs by agent, organism, and desired effect; conventional targets derived from preclinical studies are not identical to clinical targets in critically ill or immunocompromised patients. Prolonged infusion can improve target attainment when clearance is high or MIC is near the susceptibility breakpoint, but stability, line access, compatibility, and loading-dose considerations must be addressed [4,12].

3.3 Concentration-dependent activity: Cmax/MIC

Concentration-dependent killing is associated with a higher peak concentration relative to the MIC (Cmax/MIC). Aminoglycosides are the clearest clinically relevant example. A larger dose can increase the peak and bacterial killing, while a longer interval permits concentrations to fall and may reduce concentration-related toxicity. Extended-interval dosing is commonly used for selected indications, but it requires attention to kidney function, patient-specific dosing weight, infection type, and drug-level monitoring. Peak targets should not be generalized across drugs or pathogens [13,14]. In a pooled clinical analysis of 236 patients treated with gentamicin, tobramycin, or amikacin for Gram-negative infections, a higher peak-to-MIC ratio was associated with a greater likelihood of response after adjustment for illness severity. The study supports the clinical relevance of peak exposure. Monitoring still needs to account for accumulation and toxicity because a high initial peak provides limited information on subsequent clearance [13,14].

3.4 Exposure-dependent activity: AUC/MIC

The area under the concentration-time curve (AUC) summarizes total exposure over a defined interval. For antibiotics with exposure-dependent effects, the ratio of AUC to MIC is associated with efficacy. The free-drug AUC (fAUC) is often the mechanistically relevant measure, although clinical targets may use total concentrations when that is how evidence and monitoring systems were established. Fluoroquinolones, vancomycin, linezolid, and daptomycin are commonly discussed in relation to AUC/MIC, but their precise indices, targets, and toxicity relationships differ [1,4,13].

3.5 Post-antibiotic effect and bacterial regrowth

The post-antibiotic effect (PAE) is continued suppression of bacterial growth after antimicrobial concentrations fall below the MIC. Agents such as aminoglycosides and fluoroquinolones often show a meaningful PAE against susceptible

organisms, supporting dosing intervals that are not continuously above MIC. β-lactams generally have a shorter PAE against many Gram-negative bacilli, reinforcing the importance of maintaining exposure. PAE is organism- and drug-dependent and should be integrated with, rather than substituted for, the principal PK/PD index [4].

3.6 Exposure, toxicity, and resistance selection

The desired regimen balances adequate antibacterial exposure with an acceptable safety margin. Excessive exposure may cause nephrotoxicity, ototoxicity, neurotoxicity, cytopenias, or other adverse effects depending on the agent. Insufficient exposure can cause treatment failure and may favor survival of less susceptible subpopulations. The relationship is not simple: resistance selection depends on the pathogen, drug, infection burden, duration, and ecological exposure. PK/PD optimization should therefore seek an appropriate target range, not maximal drug concentration without regard to harm [5].

4. MAJOR PK/PD INDICES AND THEIR CLINICAL SIGNIFICANCE

Three principal indices organize much of antibacterial dosing practice. fT>MIC describes time above MIC; Cmax/MIC describes peak intensity relative to susceptibility; and AUC/MIC describes integrated exposure relative to susceptibility. These measures are summarized schematically in Figure 1. Their importance lies in translating a regimen into an exposure pattern that is biologically relevant for the drug class. Targets often derive from animal models, clinical pharmacology studies, or outcome analyses and may vary with infection severity and pathogen. Table 1 provides representative class associations; it is an orientation aid and not a substitute for drug-specific guidelines [1,3,4,13].

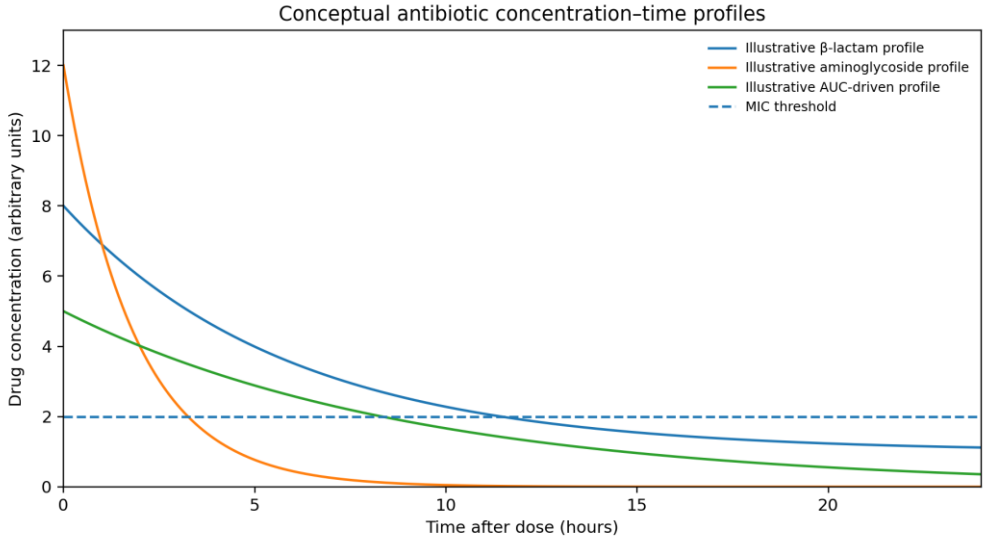

Figure 1. Conceptual antibiotic concentration–time profiles illustrating the relationship between exposure patterns and the MIC. Curves are schematic, use arbitrary units, and are not intended to represent measured pharmacokinetic data or dosing recommendations.

Table 1. Representative PK/PD drivers for selected antibiotic classes.

Antibiotic class / examples	Commonly emphasized index	Practical dosing implication
Penicillins, cephalosporins, carbapenems	fT>MIC	Frequent, extended, or continuous infusion may improve time above MIC; loading dose may be needed for continuous infusion.
Aminoglycosides (gentamicin, amikacin)	Cmax/MIC; AUC/MIC	High peak with an appropriate interval; monitor exposure and renal/ototoxic risk.
Fluoroquinolones	AUC/MIC (often also Cmax/MIC)	Ensure adequate total exposure and account for renal adjustment, interactions, and tissue penetration.
Vancomycin	AUC24/MIC	AUC-guided monitoring is preferred for serious MRSA infections where feasible.
Linezolid	AUC/MIC	Exposure relates to efficacy and hematologic toxicity; consider TDM in selected high-risk settings.
Daptomycin	AUC/MIC	Dose selection is indication-specific; monitor creatine kinase and renal function.
Macrolides	AUC/MIC or time-related exposure depending on agent/pathogen	Consider tissue accumulation, interaction potential, and agent-specific evidence.

Tetracyclines (including tigecycline)	AUC/MIC	Exposure and infection-site distribution are important; avoid class-wide extrapolation.

Abbreviations: AUC, area under the concentration–time curve; Cmax, maximum concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; fT>MIC, free-drug time above MIC. Index/targets are simplified and vary by specific agent and clinical indication [1,4,13].

5. PK/PD CHARACTERISTICS OF MAJOR ANTIBIOTIC CLASSES

5.1 β-Lactams

β-Lactams inhibit bacterial cell-wall synthesis and generally exhibit time-dependent activity. Their hydrophilic distribution, predominantly renal elimination for many agents, and relatively short half-lives make infusion strategy important. Standard intermittent dosing may be sufficient for uncomplicated infections with susceptible organisms, whereas extended infusion (often over several hours) or continuous infusion can improve fT>MIC in selected severe infections. A loading dose before continuous infusion is important to avoid a delay in attaining target exposure. In critical illness, expanded Vd and ARC can produce low concentrations; conversely, renal impairment can cause accumulation and neurotoxicity, particularly with some cephalosporins and carbapenems [2,12,15].

The DALI multicentre study demonstrated that a proportion of critically ill patients receiving β-lactams did not achieve even a conventional exposure target, and target attainment was associated with clinical outcome [15]. These findings support evaluation of exposure in high-risk patients. The 2021 Surviving Sepsis Campaign suggested prolonged β-lactam infusion for maintenance after an initial bolus. The 2026 update gives a strong recommendation, based on moderate-certainty evidence, for prolonged maintenance infusion after a loading dose in adults with sepsis or septic shock [16,17].

5.2 Aminoglycosides

Aminoglycosides disrupt bacterial protein synthesis and exhibit concentration-dependent killing with a substantial PAE for many susceptible organisms. Extended-interval regimens aim to achieve a high peak while allowing low concentrations before the next dose. Therapeutic monitoring may use peak, trough, or AUC approaches according to drug, indication, local protocol, and patient factors. Renal impairment, prolonged courses, concomitant nephrotoxins, and pre-existing auditory or vestibular risk warrant heightened caution. Dosing weight must be selected carefully in obesity, and the regimen for synergy in selected infections differs from once-daily treatment strategies. A single dosing paradigm should not be applied across all aminoglycoside indications [4,13].

5.3 Vancomycin and other glycopeptides

Vancomycin exposure is commonly related to AUC24/MIC. For serious MRSA infections, the 2020 consensus guideline recommends an AUC24 target of 400–600 mg·h/L, assuming a broth microdilution MIC of 1 mg/L. AUC-guided monitoring is favored over trough-only targeting because trough-based strategies may produce unnecessarily high exposure and nephrotoxicity [18]. Bayesian estimation or appropriately timed concentrations can support AUC estimation, though the method and sampling schedule should be validated locally. These recommendations are specific to serious MRSA infections and should not be indiscriminately extrapolated to other organisms, glycopeptides, or clinical syndromes. Other glycopeptides and lipoglycopeptides have different PK properties, half-lives, indications, and monitoring requirements. Their dosing should follow drug-specific evidence rather than a generalized vancomycin framework.

5.4 Fluoroquinolones

Fluoroquinolones inhibit bacterial DNA gyrase and topoisomerase IV. Their activity is generally associated with AUC/MIC, with Cmax/MIC also relevant. Oral bioavailability is high for several agents, allowing intravenous-to-oral transition when appropriate. Absorption can be reduced by iron, calcium, magnesium, aluminum, and other polyvalent cations; renal function and agent-specific QT, tendon, neurologic, and dysglycemia risks must be considered. Exposure optimization should not obscure important safety restrictions or the need to reserve these agents when alternatives are suitable [6,19]. A clinical PK/PD analysis of intravenous ciprofloxacin in seriously ill patients linked the 24-hour AUC/MIC ratio to microbiological and clinical outcomes. This exposure–response relationship was derived from ciprofloxacin in a particular study population. Applying it to another fluoroquinolone or infection site requires drug- and indication-specific evidence [19].

5.5 Oxazolidinones

Linezolid inhibits protein synthesis and is often described using an AUC/MIC exposure index. It has high oral bioavailability and penetrates many tissues, which can facilitate oral therapy in selected infections. Prolonged treatment can be associated with thrombocytopenia, anemia, neuropathy, and drug interactions related to monoamine oxidase inhibition. Although routine TDM is not universal, concentration assessment may be useful in prolonged courses, critical illness, renal dysfunction, or other situations where exposure and toxicity are uncertain [7,13,20]. In a retrospective cohort of 341 patients receiving linezolid, thrombocytopenia occurred in 42.9% of patients with renal impairment and 16.8% of those without it. The association persisted after adjustment. These findings support closer hematologic surveillance and exposure assessment in selected patients with impaired renal function, especially during prolonged therapy [7,20].

5.6 Macrolides, tetracyclines, and other agents

Macrolides and tetracyclines exhibit complex tissue distribution and class members differ substantially in absorption, metabolism, elimination, and PD indices. Azithromycin accumulates intracellularly and has a prolonged terminal half-life; clarithromycin has more important metabolic interactions. Doxycycline absorption may be affected by cations and administration conditions. Clindamycin, trimethoprim-sulfamethoxazole, metronidazole, and newer agents each require agent-specific interpretation of PK/PD evidence. Clinical decisions should be informed by the target pathogen, infection site, susceptibility, adverse-effect profile, and contemporary prescribing guidance rather than simplified class labels [18,21].

6. THERAPEUTIC DRUG MONITORING AND INDIVIDUALIZED DOSING

TDM involves measuring drug concentrations and interpreting them in relation to dose, timing, patient characteristics, and a therapeutic exposure goal. Its value is greatest when exposure variability is substantial, the therapeutic window is narrow, the concentration-response relationship is established, and a practical dose adjustment can be made. TDM is not equally useful for every antibiotic. It should answer a clinical question for example, whether exposure is adequate in a critically ill patient with ARC or whether an accumulation-related toxicity risk is present [13,21].

6.1 Sampling and interpretation

Sampling time must be recorded accurately, including dose and infusion start/end times. A concentration obtained at an inappropriate time may be misleading. Interpretation should account for steady state where relevant, changing renal function, recent dose changes, fluid balance, and the assay method. A measured concentration should not be acted on without understanding the pharmacokinetic model and the intended index. For vancomycin, AUC-guided approaches have become prominent for serious MRSA infection; aminoglycoside monitoring follows indication- and protocol-specific approaches; β-lactam TDM is increasingly considered for critically ill or otherwise high-variability patients, although access and target consensus remain variable [13,18,21].

6.2 Model-informed precision dosing

Model-informed precision dosing (MIPD) combines population PK models, patient covariates, measured concentrations, and Bayesian forecasting to estimate an individual's exposure and support dose adjustment. It may allow earlier target attainment with fewer samples than traditional approaches when validated software and appropriate models are available. Key limitations include model transportability across populations, incomplete covariate representation, assay and sampling quality, workflow integration, and the need for clinical oversight. MIPD is best understood as a decision-support method rather than an autonomous dosing system [21].

The TARGET randomized trial tested TDM-guided adjustment of continuously infused piperacillin–tazobactam in adults with sepsis. TDM improved attainment of the prespecified concentration target, while the mean Sequential Organ Failure Assessment score did not differ significantly between groups. Studies of dosing interventions should report both changes in exposure and patient outcomes because each addresses a different question [22].

6.3 Practical indications

TDM is particularly worth considering in severe or difficult-to-treat infections, prolonged therapy, unstable renal function, ARC, augmented or impaired drug clearance, obesity or extreme body size, burns, extracorporeal support, suspected toxicity, unexpected treatment failure, and infections caused by organisms near susceptibility breakpoints. The availability of a test, turnaround time, local expertise, and the consequence of delaying adjustment determine whether monitoring can change care [21].

7. CLINICAL IMPLICATIONS IN CRITICAL CARE AND SEPSIS

Sepsis and critical illness may alter nearly every major PK determinant. Capillary leak and fluid resuscitation can expand Vd for hydrophilic agents, lowering early plasma concentrations. Cardiac output and renal perfusion may rise or fall, leading to ARC or acute kidney injury. Vasopressors, hypoalbuminemia, extracorporeal circuits, and rapidly changing organ function further complicate exposure prediction. Standard doses can therefore result in both underexposure and accumulation over the same treatment course [2,8,15]. Early treatment requires timely administration of an appropriate empiric regimen, guided by likely pathogens, local resistance patterns, prior cultures, and infection source. Once the patient is stabilized and microbiology becomes available, therapy should be narrowed when feasible.

Prolonged infusion of β-lactams can be useful for maintaining concentrations, particularly in sepsis or infections with organisms at the upper end of susceptibility; an initial bolus/loading dose is important for continuous or extended infusion protocols. Infusion implementation should consider drug stability, line compatibility, nursing workload, and resource availability. Exposure optimization is not a substitute for reassessing diagnosis, source control, and treatment response. Persistent fever or organ dysfunction may reflect an uncontrolled source, nonbacterial cause, resistance, inadequate tissue penetration, or host factors. Escalating antibiotic dose without a structured assessment can increase toxicity while failing to address the actual cause [16].

In BLING III, 90-day mortality was 24.9% with continuous β-lactam infusion and 26.8% with intermittent infusion. The primary comparison did not reach statistical significance (absolute difference, −1.9 percentage points, 95% CI −4.9 to 1.1). Clinical cure by day 14, a secondary outcome, was more frequent with continuous infusion. A Bayesian meta-analysis of 18

randomized trials, including BLING III, estimated a 90-day mortality risk ratio of 0.86 with prolonged infusion. The pooled evidence helps explain the current guideline recommendation, and the individual trial shows the uncertainty around the size of benefit [17,23,24].

8. DOSE OPTIMIZATION IN SPECIAL POPULATIONS

8.1 Renal dysfunction and renal replacement therapy

Renal impairment commonly requires adjustment of maintenance exposure for drugs eliminated predominantly by the kidneys. The adjustment may involve dose reduction, interval extension, or both; the preferred strategy depends on the drug's PK/PD driver and clinical urgency. For time-dependent β-lactams, preserving adequate time above MIC may be important, so simply reducing each dose can compromise efficacy. For concentration-dependent agents, a suitable peak with a modified interval may be appropriate in some circumstances. Dialysis and continuous RRT remove drugs variably, and dosing must account for modality, intensity, residual kidney function, and timing. Renal function estimates are imperfect in non-steady-state acute kidney injury [2,8]. In patients receiving continuous renal replacement therapy, a change in effluent delivery or an interruption of treatment can change extracorporeal drug clearance. Residual kidney function may also change during recovery from acute kidney injury. Recording the modality and delivered therapy at the time of concentration sampling helps interpret the result and decide when exposure should be reassessed [2,8,13].

8.2 Augmented renal clearance

ARC refers to renal clearance greater than expected and may be seen in younger patients, trauma, burns, and some septic states. It can accelerate elimination of hydrophilic antibiotics and lead to subtherapeutic exposure despite apparently conventional dosing. A serum creatinine concentration within the reference range can coexist with augmented renal clearance. When suspected, measured urinary creatinine clearance, clinical context, drug concentration assessment, and dosing strategies that increase exposure may be considered according to local protocols [25,26].

8.3 Obesity and altered body composition

Obesity affects Vd and clearance in agent-specific ways; total body weight, ideal body weight, adjusted body weight, and lean body weight are not interchangeable dosing scalars. Hydrophilic agents may distribute into expanded extracellular volume, whereas lipophilic agents may show different distribution patterns. Fixed doses can underexpose some patients, but weight-based dose escalation can also cause toxicity. Drug-specific recommendations, maximum doses, renal function, and TDM should be integrated rather than applying a universal weight formula [8,25,27]. A review of antimicrobial dosing in obesity found substantial variability in both the quality of evidence and the recommended weight measures across agents. A dosing weight should therefore be selected for the specific antibiotic and indication. Assessment of renal function and, where appropriate, measured concentrations can inform subsequent maintenance dosing [27].

8.4 Pediatrics, neonates, and older adults

Maturation of renal and hepatic function, changing body composition, and age-related physiology produce distinctive PK in neonates and children. Dosing is commonly weight- or age-based but requires attention to developmental stage and indication. In older adults, reduced renal reserve, frailty, altered body composition, and polypharmacy can increase accumulation and adverse-effect risk. These populations are frequently underrepresented in exposure studies, so careful monitoring and adherence to age-specific guidance are important [25,28].

8.5 Pregnancy, burns, cystic fibrosis, and extracorporeal support

Pregnancy can increase plasma volume, renal blood flow, and glomerular filtration, while changes in protein binding and tissue distribution may alter exposure. Severe burns and cystic fibrosis can also change distribution and clearance. Extracorporeal membrane oxygenation and other extracorporeal support systems may affect PK through circuit sequestration, altered Vd, organ dysfunction, and concurrent RRT. The magnitude of change varies by drug and clinical context; broad assumptions are unreliable. Recent reviews call for better representation of these special populations in clinical pharmacology studies and more robust precision-dosing approaches [8,25,29].

Pregnancy-associated pharmacokinetic changes also vary by gestational stage and by the balance between renal elimination, metabolism, and protein binding for a given drug. Published studies frequently describe changes in maternal exposure, with fewer data linking those changes to treatment outcomes. This evidence gap limits the transfer of dosing assumptions across drugs and stages of pregnancy [25,29].

9. PK/PD-GUIDED STRATEGIES TO COMBAT ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is shaped by antibiotic exposure in patients and in microbial communities. Inadequate exposure may fail to eradicate the target pathogen and can contribute to selection of less susceptible subpopulations, while excessive or unnecessarily prolonged therapy increases ecological pressure and adverse events. PK/PD principles can support regimen selection and dose optimization, but resistance prevention also depends on infection prevention, diagnostics, stewardship, and reducing avoidable antibiotic use [4,30]. The mutant prevention concentration and the concept of a mutant selection window describe an experimentally defined exposure range in which susceptible bacteria are inhibited and less susceptible variants may persist [1,4]. Their translation into routine clinical dosing is limited by complex pathogen dynamics, uncertain clinical targets, and differences between experimental systems and human infection. These concepts

should not be used to justify unsupported dose escalation.

Stewardship programs should pair appropriate initial therapy with timely review of culture results, de-escalation, route optimization, and a documented duration. The Surviving Sepsis Campaign supports reassessment for de-escalation and shorter treatment courses in adults with sepsis or septic shock who have adequate source control. PK/PD-informed dosing therefore complements stewardship by helping ensure adequate exposure during necessary therapy while supporting cessation or narrowing when the clinical indication changes [16,17].

10. CHALLENGES AND FUTURE PERSPECTIVES

Important limitations remain. First, many PK/PD targets originate from preclinical models and may not fully represent heterogeneous human infections. Second, plasma exposure is a surrogate for concentrations at the infection site. Third, MIC measurements are subject to variability and do not describe the full bacterial population. Fourth, patient physiology can change over hours, making a dose selected at treatment initiation inappropriate later. Finally, TDM and MIPD are unevenly available, and implementation requires trained staff, validated assays, and workflow support [4,13,21].

Future development should prioritize prospective trials that link exposure optimization to patient-centered outcomes, standardized sampling and reporting, validation of targets in special populations, accessible Bayesian tools, and integration of rapid diagnostics with dosing support. Better antimicrobial susceptibility methods and models incorporating pathogen, host, and site-of-infection factors may improve prediction. Clinical decision systems should make uncertainty visible and remain subject to clinician review. The aim is not merely to achieve a numerical target, but to improve cure, reduce toxicity, and preserve antimicrobial effectiveness. Implementation also requires equity and practicality. Hospitals with limited laboratory resources may not have timely drug concentration measurements or infusion pumps for continuous delivery. PK/PD guidance should be adapted to available infrastructure without sacrificing essential principles: prompt appropriate therapy, correct dose and route, reassessment of renal function, microbiological review, source control, and rational duration [4,13,21]. Future trials should report the exposure target, how the MIC was determined, when samples were collected, and how quickly dose recommendations were implemented. Measuring these process outcomes alongside clinical cure, organ dysfunction, adverse events, and antibiotic use would help establish whether a dosing intervention improved exposure and whether that change mattered to patients [13,21,22].

11. CLINICAL PK/PD OPTIMIZATION FRAMEWORK

A structured bedside approach can help translate PK/PD concepts into practice. Figure 2 summarizes a sequence that begins with diagnosis and source control, then links agent choice and regimen to the relevant exposure index, individualizes for physiology, and ends with reassessment. The steps are iterative: changes in renal function, pathogen identification, susceptibility, or clinical response should trigger reconsideration of the regimen [8,13,17].

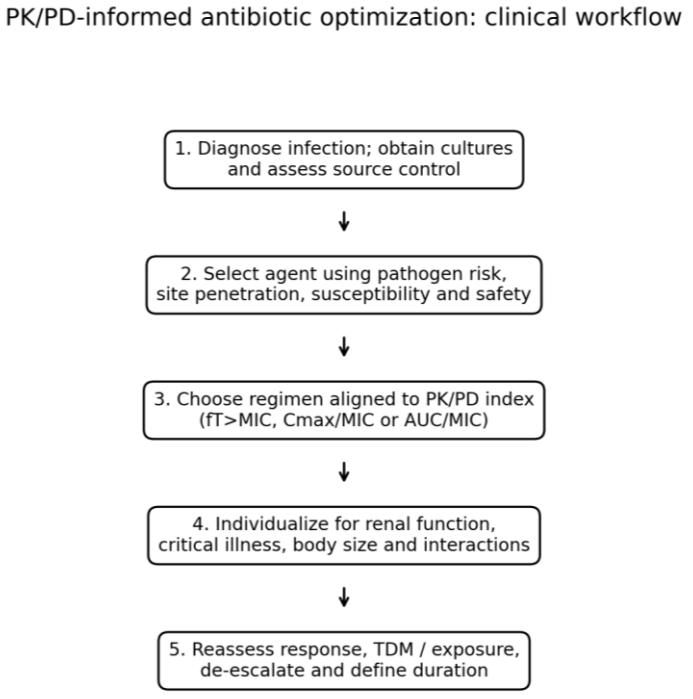

Figure 2. Original schematic of a clinical workflow for PK/PD-informed antibiotic optimization. The pathway is iterative and requires clinical judgment.

Table 2. Bedside factors that can alter antibiotic exposure and suggested responses.

Clinical factor	Potential PK effect	Possible clinical response (drug-specific)
Sepsis, capillary leak, fluid resuscitation	Expanded Vd; reduced early concentration for hydrophilic drugs	Consider loading dose when indicated; reassess exposure and response.
Augmented renal clearance	Increased elimination; underexposure	Assess renal clearance; optimize dose/interval or infusion; consider TDM.
Acute kidney injury / chronic kidney disease	Reduced clearance and accumulation	Adjust maintenance regimen; monitor renal function and drug-specific toxicity.
Obesity / extreme body size	Altered Vd and sometimes clearance	Use agent-specific weight scalar and dose limits; consider monitoring.
Hypoalbuminemia	Changed free fraction and potentially clearance/distribution	Interpret total concentrations cautiously for highly protein-bound drugs.
RRT / ECMO	Variable extracorporeal removal or circuit effects	Individualize by modality, intensity, residual function, and drug properties.
High MIC / borderline susceptibility	Greater exposure requirement; reduced probability of target attainment	Confirm susceptibility interpretation; consider alternative agent or optimized regimen under guidance.
Poor tissue penetration / inadequate source control	Insufficient local exposure despite plasma concentrations	Select site-appropriate therapy and prioritize drainage/device removal where indicated.

Responses are general principles, not patient-specific prescribing instructions [2,8,13,16].

Table 3. Practical checklist for PK/PD-guided antibiotic therapy.

Step	Clinical question	Action
1. Indication	Is bacterial infection likely and what is the source?	Obtain appropriate cultures; evaluate diagnosis and source control.
2. Agent selection	Does the agent cover likely or confirmed pathogen and reach the site?	Use local antibiogram, susceptibility data, allergy history, and site-specific guidance.
3. PK/PD driver	Which index best relates to efficacy for this drug?	Identify fT>MIC, Cmax/MIC, or AUC/MIC and drug-specific target.
4. Initial exposure	Is rapid adequate exposure needed?	Consider loading dose and suitable route/infusion strategy.
5. Patient variables	Are clearance or distribution altered?	Review renal/hepatic function, weight, fluid status, age, pregnancy, RRT, and interactions.
6. Monitoring	Would concentration measurement or MIPD change management?	Use validated TDM methods in appropriate high-risk cases.
7. Reassessment	Are microbiology and clinical response consistent with therapy?	Narrow, switch route, adjust regimen, or investigate source/diagnosis.
8. Duration	Is continued antibiotic therapy still necessary?	Set and document a syndrome-appropriate duration; reassess daily in severe infection.

This checklist is an educational synthesis and should be applied with current institutional and national guidance [13,17].

CONCLUSION

The integration of antibiotic pharmacokinetics and pharmacodynamics provides a scientific basis for selecting and optimizing antibacterial regimens. The major PK/PD indices—fT>MIC, Cmax/MIC, and AUC/MIC—describe distinct exposure drivers and should be applied according to the individual drug, pathogen, and infection context. Clinical variability arising from critical illness, renal function, body size, tissue penetration, and special populations can lead to both underexposure and toxicity. Loading doses, infusion optimization, therapeutic drug monitoring, and model-informed precision dosing may improve target attainment in selected patients, while evidence-based reassessment, de-escalation, source control, and appropriate duration remain essential. Ultimately, PK/PD-guided therapy is most effective when embedded in comprehensive clinical care and antimicrobial stewardship, with targets interpreted as decision-support tools rather than rigid rules.

Declarations

Funding
No specific funding was received for this study .

Conflict of interest

The authors declare no conflict of interest.

Ethical approval
Ethical approval was not required because this article is a narrative study and does not involve original human or animal data.

Author contributions

The lead authors and the corresponding author's supervisor prepared the first draft of the manuscript. All authors contributed to data collection, prepared the tables, critically revised the manuscript, and approved the final version for submission to the journal.

Author contributions
The authors thank the curators, indexers, and administrators of the Directory of Open Access Journals (DOAJ), Google Scholar, the Cochrane Library, PubMed, MEDLINE, Embase, and BMJ Clinical Evidence. Their work in maintaining these resources helped the authors identify and retrieve the primary studies and review articles that informed this narrative review.

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