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OPTIMISING ANTIBIOTIC DOSING IN CRITICALLY ILL PATIENTS

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Early administration of appropriate antimicrobial therapy remains a cornerstone of sepsis management; however, timely delivery of the correct antibiotic alone does not guarantee favourable outcomes in critically ill patients with sepsis. Profound and dynamically changing physiological alterations associated with critical illness result in major alterations in pharmacokinetics (PK) and may also affect tissue penetration and pharmacodynamic (PD) target attainment. Factors such as hyperdynamic circulation, capillary leak, aggressive fluid resuscitation, vasopressor use, hypoalbuminemia, augmented renal clearance (ARC), acute kidney injury, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO), and burns can substantially alter drug distribution and clearance. Consequently, antimicrobial exposure becomes highly unpredictable, particularly for hydrophilic agents such as β-lactams, aminoglycosides, and glycopeptides. Underexposure risks treatment failure and may contribute to the emergence of antimicrobial resistance, whereas overexposure increases the likelihood of drug toxicity. Standard dosing recommendations, largely derived from studies in healthy volunteers or non-critically ill populations, often fail to achieve optimal pharmacokinetic/pharmacodynamic (PK/PD) targets in critically ill patients, highlighting the need for individualized antibiotic dosing strategies.

Optimizing antibiotic dosing requires a precision medicine approach that considers the patient-drug-pathogen interplay, which is profoundly altered in critically ill patients with sepsis. For hydrophilic antimicrobials, initial dosing should compensate for expanded volumes of distribution using loading doses, which are generally determined by the volume of distribution rather than renal function. Maintenance dosing must then be adjusted according to dynamic changes in organ function and drug clearance. Alternative administration strategies, including extended or continuous infusions of time-dependent antibiotics such as β-lactams, can improve PK/PD target attainment and may improve clinical outcomes, particularly in patients with severe infections, high pathogen minimum inhibitory concentrations (MICs), or markedly altered PKs. Therapeutic drug monitoring (TDM) further enables individualized dose adjustment by integrating measured antibiotic concentrations with PK/PD targets, helping to maximize efficacy while minimizing toxicity. Emerging approaches such as model-informed precision dosing (MIPD) offer promising opportunities to advance personalized antimicrobial therapy, although widespread implementation in routine clinical practice remains limited.

Antibiotic dosing optimization should be regarded as a fundamental component of antimicrobial stewardship. A structured approach involving early assessment, individualized dosing, therapeutic monitoring, incorporation of pathogen susceptibility and MIC data when available, and continuous reassessment can improve target attainment, reduce toxicity, limit resistance emergence, and enhance clinical outcomes. In critically ill patients, one dose does not fit all; precision dosing is essential to deliver effective and safe antimicrobial therapy.

Keywords:
Critical illness; Antibiotic dosing optimization; Pharmacokinetics/Pharmacodynamics (PK/PD); Therapeutic drug monitoring (TDM); Precision dosing