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THE IMPACT OF PATHOPHYSIOLOGICAL ALTERATION ON DRUG EFFECTS DURING CRITICAL ILLNESS

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Background: Critically ill patients are at high risk for development of life-threatening infection leading to sepsis and multiple organ failure. Adequate antimicrobial therapy is pivotal for optimizing the chances of survival. Dosing guidelines used in the Intensive Care Unit (ICU) are frequently extrapolated from healthy volunteers or stable patient populations. However, critical illness triggers severe, dynamic pathophysiological shifts that fundamentally disrupt standard pharmacokinetic (PK) and pharmacodynamic (PD) profiles, that invalidate these standard assumptions, frequently resulting in sub-therapeutic or toxic drug concentrations. **Objective:** This paper evaluates how critical illness-induced alterations—specifically capillary leak, fluid resuscitation, organ failure—impact the systemic exposure and therapeutic efficacy of essential medications.

Methods: A comprehensive review of recent clinical trials and observational data was conducted, evaluating PK/PD parameter variations (volume of distribution (Vd), clearance (CL), plasma protein binding) across various classes of critical care medications, with an emphasis on hydrophilic antimicrobials, sedatives, anticoagulants, and vasoactive agents. **Results:** The systemic inflammatory response syndrome (SIRS) and endothelial dysfunction cause significant capillary leaking. When paired with aggressive fluid resuscitation, this drastically increases Vd of hydrophilic drugs, causing immediate plasma underdosing. Augmented renal clearance (frequently observed in early hyperdynamic sepsis) accelerates the elimination of renal-cleared medications, concurrently, states of cardiac hyperperfusion and the use of inotropes can trigger enhanced renal clearance (ARC), accelerating drug elimination and dropping concentrations below therapeutic thresholds. Conversely, subsequent acute kidney injury (AKI), hepatic hypoperfusion, and down-regulated cytochrome P450 activity significantly reduce drug clearance, elevating the risk of toxicity. Altered splanchnic blood flow and changes in gastric pH compromise enteral absorption. Critical illness also markedly reduces plasma albumin levels,

shifting the free-fraction of highly protein-bound medications unpredictably. **Conclusion:** Standard, unadjusted dosing protocols fail a significant portion of critically ill patients due to high inter- and intra-individual PK/PD variability. Individualizing drug therapy through Therapeutic Drug Monitoring (TDM), extended or continuous infusions, and patient-specific loading doses is essential to optimize clinical outcomes in the Intensive Care Unit (ICU).

Keywords: Organ failure; Intensive care unit; Pharmacodynamics; Pharmacokinetics.