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Drug Dosing and Adjustments During CRRT

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Continuous renal replacement therapy (CRRT) significantly impacts drug pharmacokinetics (PK) and pharmacodynamics (PD) in critically ill patients, necessitating careful adjustments to medication dosing to maintain therapeutic efficacy and prevent treatment failure. CRRT alters drug clearance through distinct filtration and diffusion mechanisms compared to normal renal excretion, influenced primarily by drug characteristics such as protein binding, molecular weight, and volume of distribution (Vd). Drugs with low protein binding and smaller molecular sizes are more readily removed during CRRT, while medications with low Vd, primarily intravascular, experience higher clearance. Pharmacodynamic considerations during CRRT must account for its continuous nature, significantly affecting both time-dependent and concentration-dependent antimicrobials. Time-dependent antibiotics require sustained drug concentrations above the minimum inhibitory concentration (MIC), whereas concentration-dependent antimicrobials necessitate achieving optimal peak concentrations relative to MIC. Inappropriate dosing adjustments can result in subtherapeutic levels, increasing the risk of antimicrobial resistance and clinical failure. Drug clearance during CRRT is influenced by both therapy-specific and patient-specific factors. CRRT mode, effluent flow rate, membrane characteristics, and adsorption properties significantly impact drug elimination. High-flux membranes facilitate increased clearance of larger molecules, while drug adsorption complicates pharmacokinetic predictions. Additionally, patient-specific variables, including residual renal function and physiological alterations related to critical illness (e.g., hypoalbuminemia, increased cardiac output), further affect drug distribution and elimination, necessitating individualized dosing approaches. Clinical strategies to address these challenges emphasize aggressive initial dosing akin to normal renal function, with subsequent maintenance dose adjustments based on clearance profiles and patient residual renal function. Loading doses should remain unchanged due to their dependency on volume of distribution, whereas maintenance regimens require modification according to CRRT-specific clearance dynamics. Extended or

continuous infusions of beta-lactams, such as piperacillin-tazobactam, demonstrate improved therapeutic outcomes compared to intermittent dosing. Aminoglycosides require larger loading doses due to increased clearance, and therapeutic drug monitoring (TDM) is particularly essential for medications like vancomycin and aminoglycosides to ensure optimal therapeutic ranges. Therapeutic drug monitoring remains a critical component for managing variability in drug pharmacokinetics during CRRT, especially for agents with narrow therapeutic indices. Population pharmacokinetic models and Monte Carlo simulations are useful tools when TDM is not feasible, guiding dosing adjustments and ensuring efficacy and safety. In conclusion, optimal drug therapy during CRRT requires integrating comprehensive knowledge of pharmacokinetic and pharmacodynamic changes, therapy-specific variables, and patient-specific factors. Clinicians should proactively apply evidence-based dosing strategies, closely monitor therapeutic outcomes, and dynamically adjust dosing to optimize treatment efficacy and reduce the risk of treatment failure and antimicrobial resistance.

Keywords: Continuous renal replacement therapy, pharmacokinetics, pharmacodynamics, therapeutic drug monitoring , critical illness