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We Underdose Antibiotics in Patients on CRRT

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ABSTRACT

Appropriate antibiotic dosing in critically ill, infected, patients receiving continuous renal replacement therapy (CRRT) is crucial to improve patient outcomes. Severe sepsis and septic shock result in changes in pharmacokinetic parameters, including increased volume of distribution, hypoalbuminemia, and changes in renal and nonrenal clearances. The lack of CRRT standardization, nonrecognition of how CRRT variability affects antibiotic removal, fear of antibiotic toxicity, and limited drug dosing resources all contribute to suboptimal antibiotic therapy. Even when antibiotic CRRT pharmacokinetic studies are available, they are often based on old CRRT methodologies that do not exist in contemporary CRRT practice, resulting in unhelpful/inaccurate dosing recommendations. Application of these older doses in Monte Carlo simulation studies reveals that many of the recommended dosing regimens will never attain pharmacodynamic targets. In this review, using cefepime as an example, we illustrate whether clinicians are likely to achieve pharmacokinetic/pharmacodynamic targets when the recommended dosing regimens are prescribed in this patient population. We encourage clinicians to aggressively dose antibiotics with large loading dose and higher maintenance doses to reach the targets.

Continuous renal replacement therapy (CRRT) has been used for acute kidney injury (AKI) management in hemodynamically unstable critically ill patients. CRRT prescriptions differ in the type of modalities, hemofilters, and effluent flow rates, all of which may profoundly affect antibiotic dosing. The wide variety of clinically used CRRT settings results in a subsequent lack of uniformity in antibiotic dosing (1). Although KDIGO guidelines (2) recommend an effluent rate of 20–25 ml/kg/hour for CRRT in AKI treatment, ICU physicians most commonly prescribe initial effluent flow rates that are even higher (25–35 ml/kg/hour) (3). Even if the delivered CRRT dose is less than prescribed, "standard" antibiotic dosing conducted at KDIGO-effluent rates is often nontherapeutic (4) and the use of even higher effluent rates would require even higher daily antibiotic doses. The septic patient receiving CRRT desperately needs antibiotics dosed to therapeutic levels, but many barriers exist to ever achieving this goal (5). As a result, we frequently underdose antibiotics in patients on CRRT.

Severe sepsis and septic shock are among the two most common reasons for CRRT initiation. Proper antibiotic dosing is crucial to minimize the morbidity and mortality associated with sepsis (6). Patients with sepsis or septic shock often present with a variety of physiologic abnormalities that often preclude effective antibiotic dosing. Inflammatory mediators released during the immune response result in increased capillary permeability leading to fluid accumulation and hypoalbuminemia (7). Sepsis also results in acute kidney and liver injury, however, a patient with AKI may still have well-preserved nonrenal (hepatic) drug clearance (5). These physiologic changes alter the pharmacokinetic parameters that must be considered for proper antibiotic dosing.

The most important pharmacokinetic factors to consider in patients receiving CRRT are a drug's volume of distribution, protein binding and metabolism. Fluid accumulation due to medication, nutrition, and blood product administration, fluid resuscitation and increased capillary permeability causes an increase in the volume of distribution of water soluble drugs. Through dilution, a reduction in antibiotic concentration in the plasma and at the site of infection will be seen. The extent of fluid overload is most prominent during the initial stages of severe sepsis but declines during the course of treatment due to the normalization of the physiologic changes and from fluid removal by CRRT (7). Hypoalbuminemia has been reported in 40–50% of critical care patients (8) and can have a large effect on the amount of free (unbound) drug that has pharmacologic activity. However, the increase in free drug allows for more drug to be distributed into the interstitial space and more free drug that

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can be cleared by the liver, kidneys, and RRT yielding a lower than expected antibiotic concentration at the site of infection. Concomitant medications, such as vasoactive agents, alter the hemodynamic state of the patient and potentially hepatic and renal drug clearance. While the potential for antibiotic toxicity should be considered, based on these pharmacokinetic changes, the prudent approach to antibiotic dosing should be an aggressive one, especially in early sepsis, to ensure that optimal antibiotic concentrations are obtained.

Available clinical resources used to recommend antibiotic dosing in critically ill patients receiving CRRT often results in suboptimal therapy (4). These clinical resources that developed dosing recommendations usually were based on few pharmacokinetic studies and limited dosing information provided in package inserts. In addition, those cited studies often used conservative CRRT effluent rates and techniques that are now outdated. Interestingly, most of the studies incompletely report key pharmacokinetic information to design proper dosing regimens for patients receiving CRRT (9). Applying these dosing recommendations to critically ill patients with modern CRRT settings must be reconsidered.

Pharmacodynamic target attainment is associated with enhanced antimicrobial activity and improved patient outcomes. Antibiotics can be divided into two different categories; concentration-dependent or time-dependent killing activity (7). The increasing antibiotic resistance in the ICU requires even more aggressive antibiotic dosing to reach pharmacodynamic goals (7). Consequently, evidence is building that older dosing recommendations do not meet the contemporary pharmacodynamic targets. Seyler et al. revealed that the recommended doses of β-lactams for patients receiving CRRT with *Pseudomonas aeruginosa* infection were generally not adequate to attain pharmacodynamic targets in the first 48 hours of therapy (4). Roberts et al. similarly report that usual empirical dosing of antibiotics in severely ill patients with CRRT failed to reach targets (10). The need for more aggressive antibiotic dosing in CRRT has been shown even for a very old drug that is routinely monitored, vancomycin, at effluent rates below KDIGO recommendations. In critically ill patients undergoing CVVH with ultrafiltration rates of 12–18 ml/kg/minute, larger than usual vancomycin doses (500–750 mg every 12 hours) were required to attain appropriate drug exposure targets (11). The recommended antibiotic doses in these patients must be reevaluated and aggressive antibiotic dosing should be prescribed to achieve pharmacokinetic and pharmacodynamic targets.

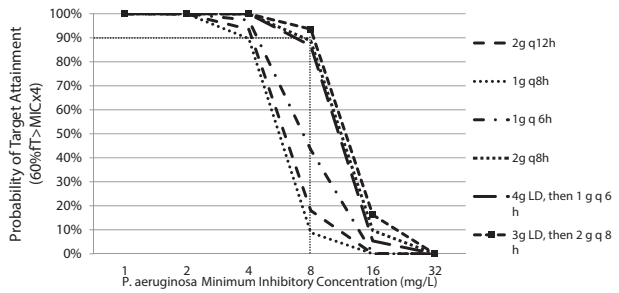

FIG. 1. Pharmacodynamic target attainment for modeled cefepime regimens in simulated patients receiving CVVHDF therapy with 25 ml/kg/hour effluent flow rate for the first 48 hours of therapy.

How poorly do clinicians dose antibiotics in CRRT? We can use cefepime as an example of a commonly prescribed antibiotic in this setting where we can estimate the likelihood of achieving therapeutic dosing using Monte Carlo simulations. Simulations using known pharmacokinetic, demographic, and CRRT data allow for experimentally "dosing" these virtual CRRT patients with cefepime to see if pharmacodynamic targets are attained. For example, we know the weight (mean ± SD kg) of the typical American ICU patient receiving RRT and the mean ± SD pharmacokinetic parameters of cefepime in critical illness and its clearance by CRRT. If we "create" 5000 virtual patients within the weight range of known CRRT patients and administer varying doses of cefepime and CRRT, we can determine the cefepime concentration-time profiles for each of these patients. By examining these profiles, we can identify whether the administered doses are likely to attain pharmacodynamic targets.

Published cefepime dosing recommendations for patients with CRRT range from 2 to 4 g/day. We tested these doses using Monte Carlo simulations as described above. Patients who were the size of the typical American ICU patient receiving CVVHDF at KDIGO-effluent rates (25 ml/kg/hour) were "given" differing doses of cefepime. Optimal cefepime regimens were defined as dosing regimens that achieved ≥90% of probability of pharmacodynamic target attainment, defined as a plasma concentration four times the MIC for sensitive *Pseudomonas aeruginosa* of 8 mg/l (32 mg/l) (12) for at least 60% of the dosing interval. Figure 1 illustrates that none of the published recommended cefepime regimens reached pharmacodynamic targets associated with antibiotic cure. The optimal regimen in the first 48 hours with the smallest daily dose was a loading dose of 3 g followed by a maintenance dose of 2 g every 8 hours. This "therapeutic" dosing regimen is higher than the recommended doses for patients on CRRT and even patients with normal renal function. The need for a higher dose could be explained by the impact of increased volume of distribution, unrecognized nonrenal clearance and CRRT removal in critically ill patients. Validation of the results is necessary to determine antibiotic efficacy in real-life situations and prevent adverse effects from aggressive dosing.

As a result of the "over-prevalent underdosing" (5) of patients receiving CRRT, we must rethink the fear of antibiotic toxicity from prescribing high doses in renal impairment. The above cefepime Monte Carlo simulations demonstrate that the most

common resources used to dose patients receiving CRRT result in inadequate cefepime concentrations and fail to reach established pharmacodynamic targets. If cefepime is indicative of other antibiotics also not achieving therapeutic levels in CRRT patients, and evidence suggests it is (4,10), then it should not surprise us that CRRT patients are far more likely to die of infection than any other cause (13). To ensure therapeutic doses in these complicated patients, antibiotic administration should consist of an initial loading dose and "larger than conventional" maintenance doses. Most patients in the ICU do not reach pharmacodynamic targets or experience adverse effects due to antibiotic toxicity (7), and it appears likely that we are putting patients at higher risk of infectious death with the current antibiotic dosing patterns. The evidence is increasingly compelling that to reduce mortality and reach pharmacokinetic-pharmacodynamic targets in this population we must reconsider the one size fits all mentality and move forward to an aggressive approach to antibiotic dosing. Let's stop underdosing antibiotics in patients receiving CRRT!

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The authors declare that they have no relevant financial interests.

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