Editorial

Antibiotic Dosing in Critically Ill Patients Receiving CRRT: Underdosing is Overprevalent

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ABSTRACT

Published CRRT drug dosing algorithms and other dosing guidelines appear to result in underdosed antibiotics, leading to failure to attain pharmacodynamic targets. High mortality rates persist with inadequate antibiotic therapy as the most important risk factor for death. Reasons for unintended antibiotic underdosing in patients receiving CRRT are many. Underdosing may result from lack of the recognition that better hepatic function in AKI patients yields higher nonrenal antibiotic clearance compared to ESRD patients. Other factors include the variability in body size and fluid composition of patients, the serious consequence of delayed achievement of antibiotic pharmacodynamic targets in septic patients, potential subtherapeutic antibiotic concentrations at the infection site, and the influence of RRT intensity on antibiotic concentrations. Too often, clinicians weigh the benefits of overcautious antibiotic dosing to avoid antibiotic toxicity too heavily against the benefits of rapid attainment of therapeutic antibiotic concentrations in critically ill patients receiving CRRT. We urge clinicians to prescribe antibiotics aggressively for these vulnerable patients.

"Without reflection, we go blindly on our way, creating more unintended consequences, and failing to achieve anything useful."

Margaret J. Wheatley

Finding Our Way: Leadership For an Uncertain Time (2005) p. 262

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Continuous renal replacement therapy (CRRT) has been universally accepted as a preferred treatment for acute kidney injury (AKI) and fluid overload since first being described in 1977 (1). CRRT has been studied from so many angles, (machine design, therapy delivery, anticoagulation, vascular access, economics, clinician education, etc.) and as a result, its usage has become routine. In general, we have done a good job of designing an effective system for controlling azotemia, balancing electrolytes, and removing fluid. In treating these critically ill patients with very high mortality rates with CRRT

and other RRTs employed in the ICU, clinicians are often quite judicious when it comes to antibiotic dosing, and with good reason. Most antibiotics are cleared by the kidney, and dosage reduction is necessary in renal disease to prevent drug and metabolite accumulation. Further, many of these agents are nephrotoxic themselves, and concerns of prolonging AKI are legitimate. However, the combination of very efficient RRTs and concerns about giving excessive doses has in our opinion, resulted in an unintended consequence of antibiotic underdosing in many (most?) patients receiving CRRT. As mentioned in the quote that leads this article, it is time for some reflection on this unintended consequence if we are going to achieve anything useful.

Antibiotic Pharmacotherapy in CRRT circa 2014

Sepsis is a common cause of AKI in critically ill patients, with 70% of those requiring some type of renal replacement therapy (RRT) (2). Adequate antibiotic dosing is essential to minimize the morbidity and mortality of sepsis, but is very challenging due to the complexity associated with underlying diseases and their unpredictable impact on pharmacokinetic properties of drugs. Variance in RRT modalities and regimens and a discrepancy between prescribed and delivered RRT regimens can further compound the issue. No prospectively

validated guidelines exist to aid antibiotic dosing for these patients. Clinicians frequently consult renal dosing references or software programs such as Micromedex for help. However, these recommended doses are often based on in vitro studies, case reports, or very small clinical pharmacokinetic trials often using obsolete CRRT technologies or techniques. Often the recommendations are extrapolated from pharmacokinetic data obtained in noncritically ill patients or patients with end stage renal disease (ESRD) receiving other renal replacement therapies (3). Published clinical pharmacokinetic experience usually lacks vital information necessary to apply published results to patient care (4,5).

Given the myriad of potential combinations of diffusion, convection, flow rates, filters, patient characteristics, and co-morbidities that are found in clinical practice and the highly variable pharmacokinetic characteristics in critically ill patients, most published guidelines have limited applicability to clinical practice. The evidence suggests that despite the availability of many published CRRT drug dosing guidelines, we rarely meet pharmacodynamic targets for antibiotics (6–9), and patient mortality rates remain grim with inadequate antibiotic therapy as the most important risk factor for death (10).

Because CRRT uses a pump running at a constant setting to generate spent dialysate and ultrafiltrate, some have taken a more mathematical approach toward determining appropriate antibiotic dosing. Various dosing equations for critically ill patients receiving CRRT have been published. These also have not been prospectively validated, but the idea that antibiotic dosing regimens could be created if you had an understanding of drug removal by the CRRT system was a logical approach. To determine the merit of this approach, we compared the antibiotic doses calculated from three different published drug dosing equations in CRRT [Kroh (11), Reetze-Bonorden (12), and Bugge (13)] to one another and to doses from a commonly used renal dosing book [Aronoff et al. (14)] for a hypothetical 70 kg anuric adult receiving CRRT with the KDIGO recommended effluent rate of 25 ml/minute (21.4 ml/kg/hour). Necessary pharmacokinetic data were obtained from published literature and manufacturer data.

Table 1 illustrates the wide variability found in calculated antibiotic doses with the 3 equations and the recommended doses from the Aronoff text. For example, the calculated doses of piperacillin ranged 5,370–11,181 mg/day, while the Aronoff text suggests a dose of 12,000 mg/day. These published equation-based techniques make mathematical sense, in that doses rise as effluent rates rise, and presumably underwent thorough peer review to evaluate their suitability. On the basis of their "logic" and the fact that they have appeared in print, clinicians could reasonably choose any one of these as the basis of their antibiotic dosing in their practices. We are aware that each of these approaches are used in clinical settings around the

TABLE 1. Comparison of recommended antibiotic dosing by 4 different resources for a hypothetical 70 kg anuric adult receiving CRRT with the effluent rate of 25 ml/minute (11–14)

Antibiotics	Aronoff (mg/day)	Kroh (mg/day)	Reetze-Bonorden (mg/day)	Bugge (mg/day)
Cefepime	4,000	2,150	935	2,363
Daptomycin	280	328	378	242
Linezolid	1,200	797	1,526	770
Meropenem	3,000	1,227	1,899	1,477
Piperacillin	12,000	5,370	11,181	6,882

globe, with some clinicians having gone so far as developing an "app" on their smartphones to do the calculations for them. In contrast, authors of the Aronoff text (disclosure: BAM was an author on Aronoff text) applied pharmacokinetic data from CRRT trials to develop an antibiotic's dose which was determined by consensus with a group of CRRT experts examining the data.

Despite the "rationality" of any of these approaches, more recent literature suggests that we are missing the dosing mark by a wide margin. For example, in the aforementioned piperacillin example, the calculated dose range of 5,370–12,000 mg/day contrasts with the data from Seyler et al. who found that 16,000 mg/day of piperacillin (in the form of piperacillin/tazobactam) met defined antibiotic pharmacodynamic targets in only 71% of patients receiving CRRT with a mean effluent rate of ~45 ml/kg/hour (6). Although Seyler et al. used an aggressive pharmacodynamic target and a higher effluent rate, the evidence increasingly suggests that nearly everything clinicians think they know about therapeutic antibiotic dosing in patients receiving CRRT needs rethinking.

Why Might Antibiotic Underdosing Be "Overprevalent"?

When we reflect on what we learned in our years of training as pharmacists, we find that much of what we had been taught about antibiotic dosing in this patient population was probably wrong. In the early years of CRRT, we were taught to use the sieving coefficient of the drug and calculate CRRT clearance. We simply replaced the amount of cleared drug with an adjusted antibiotic dose, without consideration of the many pharmacokinetic differences between ESRD patients and critically ill AKI patients. Pharmacists were trained to aggressively lower antibiotic doses in patients with kidney disease to avoid antibiotic toxicity and to reduce drug cost (15). However, a balance needs to be struck between concerns of toxicity that limits the dose and the understanding of altered pharmacokinetics in critically ill patients that requires larger doses.

Besides the fact that blind reliance on any published dosing resource can be problematic, what are

some of the things we think we know about antibiotic dosing that are also probably wrong?

1. The degree or characteristics of pharmacokinetic alteration in critically ill patients with AKI should not be presumed to be the same as those with ESRD. For example, patients with AKI may, for unclear reasons, exhibit relatively higher nonrenal clearance which can significantly remove several antibiotics including imipenem, meropenem, and vancomycin (16–18), compared with those with ESRD. Thus, patients with AKI may require a higher antibiotic dosage than those with ESRD.

2. The usage of "one-size-fit-all" dosing strategy (e.g., a fixed dose, regardless of body mass) carry bias due to lack of integration of the variability in body sizes and body fluid compositions of patients. Patients with AKI often exhibit a larger drug volume of distribution due to sepsis, fluid overload, and obesity. We recently reviewed data on 94 consecutive patients receiving CRRT in our institution's ICUs in 2011. We found that the median [IQR] patient weight was 101.5 kg [84–134 kg] at CRRT initiation. It is likely that manufacturer-recommended antibiotic doses were not derived from subjects > 100 kg. One-size-fit-all or flat antibiotic dosing may not achieve serum concentration goals in these large patients. Increased body mass index is reported as a significant risk factor of antibiotic therapy failure (19). Thus, it may be prudent to employ weight-based dosing regimens in cases where a patient's body size and fluid composition deviate from the normal ranges.

3. Increasing evidence of an association between initially low serum antibiotic concentrations/suboptimal antibiotic therapy and a decrease in pathogen susceptibility suggest the necessity of early attainment of pharmacodynamic goals (20,21). In contrast to our current, relatively cautious antibiotic dosing practices in patients with AKI, higher antibiotic dosing may be necessary initially to reduce the incidence of antibiotic resistance. Accounting for constant extracorporeal drug removal via CRRT and altered pharmacokinetics, very large initial doses may be needed to maximize therapeutic efficacy. Utilization of a loading dose may be beneficial not only in antibiotics with concentration-dependent killing (e.g., aminoglycosides) to achieve a higher initial peak, but also those with time-dependent killing (e.g., beta-lactams, vancomycin) to allow target serum concentration to be reached as early as possible. Most clinicians never use an antibiotic loading dose in these patients.

4. "Adequate" concentrations in the serum should not be interpreted as an equivalent concentration at the actual sites of infection which mostly occurs in tissues. Impaired tissue penetration because of altered pathophysiology and transporter activity in this population may result in a subtherapeutic infection site concentration despite a "therapeutic" serum concentration (22–24). The same clinicians that generally recognize the difficulty of getting adequate local antibiotic concentrations in diabetic foot infections don't often consider similar challenges in massively edematous AKI patients. Until novel methods to measure drug concentrations at the infection site such as microdialysis (25) become available, higher antibiotic doses may be warranted to ensure adequate antibiotic therapy.

5. The influence of RRT dose intensity must be taken into account when designing an antibiotic dosing regimen. Over the past decade, the most common CRRT debate has been about CRRT dose intensity. The early report from Ronco suggested that high volume CVVH was superior to lower doses (26). In contrast, this study was followed by very large multicenter trials (27–29) that consistently found that patient outcomes did not differ between more aggressive and less aggressive CRRT. The nephrology and critical care community appears to have embraced this view, and guidelines have been published that recommend relatively low intensity CRRT (30). However, as Kielstein has opined, the study designs of the trials comparing high and low intensity CRRT had one common flaw: patients in both CRRT groups received the same antibiotic doses (31,32). Consequently, not only were these studies comparing high and low CRRT intensity, but they were also comparing lower antibiotic serum concentrations (high intensity) vs. higher antibiotic serum concentrations (low intensity). If appropriate antibiotic dosing and antibiotic exposure is important in septic patient outcomes, and the evidence suggests that it is (10, 33), then it is quite interesting that patient outcomes with high intensity CRRT were not inferior to low intensity CRRT. If one follows this line of logic, it opens up an entirely new perspective. Would high CRRT intensity have better patient outcomes if antibiotic serum concentrations/antibiotic exposure was kept equal between the groups? More aggressive CRRT means more rapid antibiotic removal (34), but because we cannot routinely measure serum levels of most antibiotics, we generally cannot discern inadequate antibiotic exposure.

Toward More Appropriate Antibiotic Dosing

When we address this issue in national forums, we routinely ask the audience the following two questions:

1. Of the last 10 CRRT patients you treated, how many exhibited signs or symptoms of receiving too much antibiotic?
2. Of the last 10 CRRT patients you treated, how many died of infection?

Invariably, the answer to question 1 is zero. Because sepsis is such a prevalent diagnosis in CRRT patients, the answer to question 2 is generally two to three deaths. This consistent response may be related to the high infection-related mortality rate seen in the ICU. These rates have not improved much since the advent of CRRT despite substantial advances in CRRT technologies and improved understanding of antibiotic pharmacokinetics/pharmacodynamics. Reappraisal of the evidence as outlined in this paper challenge commonly held beliefs regarding antibiotic dosing in CRRT patients. Our too-careful practice of "starting low and going slow" with antibiotic dosing to avoid the risk of antibiotic toxicity may lead to an unintended consequence that is far more harmful to patients. We believe that commonly held misconceptions of antibiotic dosing in CRRT are partially responsible for an "overprevalence" of antibiotic underdosing and call for clinicians to reflect on their current practices to strike a more aggressive antibiotic prescription in the intensive care unit so that we can achieve something "useful".

Conflicts of Interest

Lewis: No conflicts of interest to report. Mueller: Speakers Bureau: Cubist Pharmaceuticals, Gambro.

References

1. Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F: Arteriovenous haemofiltration: a new and simple method for treatment of over-hydrated patients resistant to diuretics. *Klin Wochenschr* 55(22):1121–1122, 1977
2. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Septic Acute Kidney Injury in Critically Ill Patients: Clinical Characteristics and Outcomes. *Clin J Am Soc Nephrol* 2(3):431–439, 2007
3. Mueller BA, Smoyer WE: Challenges in developing evidence-based drug dosing guidelines for adults and children receiving renal replacement therapy. *Clin Pharmacol Ther* 86(5):479–482, 2009
4. Li AM, Gomersall CD, Choi G, Tian Q, Joynt GM, Lipman J: A systematic review of antibiotic dosing regimens for septic patients receiving continuous renal replacement therapy: do current studies supply sufficient data? *J Antimicrob Chemother* 64(5):920–937, 2009
5. Vaara S, Pettila V, Kaukonen KM: Quality of pharmacokinetic studies in critically ill patients receiving continuous renal replacement therapy. *Acta Anaesthesiol Scand* 56(2):147–157, 2012
6. Seyler L, Cotton F, Taccone S, De Backer D, Macours P, Vincent JL, Jacobs F: Recommended B-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. *Crit Care* 15:R137, 2011
7. Wilson FP, Berns JS: Vancomycin levels are frequently subtherapeutic during continuous venovenous hemodialysis (CVVHD). *Clin Nephrol* 77(4):329–331, 2012
8. Vilay AM, Grio M, DePestel DD, Sowinski KM, Gao Lihong, Heung M, Salama NN, Mueller BA: Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. *Crit Care Med* 39:19–25, 2011
9. Afshartous D, Bauer SR, Connor MJ, Aduroja OA, Amde M, Salem C, Groszek JJ, Fissell WH: Pharmacokinetics and pharmacodynamics of imipenem and meropenem in critically ill patients treated with continuous venovenous hemodialysis. *Am J Kidney Dis* 63(1):170–171, 2014
10. Kollef MH, Sherman G, Ward S, Fraser VJ: Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 115(2):462–474, 1999
11. Kroh UF: Drug administration in critically ill patients with acute renal failure. *N Horiz* 3(4):748–759, 1995
12. Reetze-Bonorden P, Böhler J, Keller E: Drug dosage in patients during continuous renal replacement therapy. Pharmacokinetic and therapeutic considerations. *Clin Pharmacokinet* 24(5):362–379, 1993
13. Bugge JF: Pharmacokinetics and drug dosing adjustments during continuous venovenous hemofiltration or hemodiafiltration in critically ill patients. *Acta Anaesthesiol Scand* 45:929–934, 2001
14. Aronoff GR, Bennett WM, Berns JS, Brier ME, Kasbekar N, Mueller BA, Pasko DA, Smoyer WE: *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th edn. Philadelphia, PA: American College of Physicians, 2007
15. Abel SR, Guba EA: Evaluation of an imipenem/cilastatin target drug program. *DICP* 25(4):348–350, 1991
16. Mueller BA, Scarim SK, Macias WL: Comparison of imipenem pharmacokinetics in patients with acute or chronic renal failure treated with continuous hemofiltration. *Am J Kidney Dis* 21:172–179, 1993
17. Ververs TF, van Dijk A, Vinks SA, Blankestijn PJ, Savelkoul JF, Meulenbelt J, Boereboom FT: Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous venovenous hemofiltration. *Crit Care Med* 28:3412–3416, 2000
18. Macias WL, Mueller BA, Scarim SK: Vancomycin pharmacokinetics in acute renal failure: preservation of nonrenal clearance. *Clin Pharmacol Ther* 50:688–694, 1991
19. Longo C, Bartlett G, Macgibbon B, Mayo N, Rosenberg E, Nadeau L, Daskalopoulou SS: The effect of obesity on antibiotic treatment failure: a historical cohort study. *Pharmacoepidemiol Drug Saf* 22:970–976, 2013
20. Martinez MN, Papich MG, Drusano GL: Dosing regimen matters: the importance of early intervention and rapid attainment of the pharmacokinetic/pharmacodynamic target. *Antimicrob Agents Chemother* 56(6):2795–2805, 2012
21. Jumbe N, Louie A, Leary R, Liu W, Deziel MR, Tam VH, Bachhawat R, Freeman C, Kahn JB, Bush K, Dudley MN, Miller MH, Drusano GL: Application of a mathematical model to prevent *in vivo* amplification of antibiotic-resistant bacterial populations during therapy. *J Clin Invest* 112(2):275–285, 2003
22. Joukhadar C, Frossard M, Mayer BX, Brunner M, Klein N, Siostrzonek P, Eichler HG, Müller M: Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. *Crit Care Med* 29(2):385–391, 2001
23. Ryan DM, Cars O: A problem in the interpretation of beta-lactam antibiotic levels in tissues. *J Antimicrob Chemother* 12(3):281–284, 1983
24. Schentag JJ, Heller AS, Hardy BG, Wels PB: Antibiotic penetration in liver infection: a case of tobramycin failure responsive to moxalactam. *Am J Gastroenterol* 78(10):641–644, 1983
25. Müller M: Monitoring tissue drug levels by clinical microdialysis. *Altern Lab Anim* 37(1):57–59, 2009
26. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 356(9223):26–30, 2000
27. Vesconi S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monti G, Marinho A, Mariano F, Formica M, Marchesi M, René R, Livigni S, Ronco C; DOse REsponse Multicentre International collaborative Initiative (DO-RE-MI Study Group): Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. *Crit Care* 13(2):R57, 2009
28. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 359(1):7–20, 2008
29. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 361 (17):1627–1638, 2009
30. Kellum JA, Lamiere N: KDIGO clinical practice guideline for acute kidney injury. Available at http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf. accessed Jan 2, 2014
31. Kielstein JT, Burkhardt O: Dosing of antibiotics in critically ill patients undergoing renal replacement therapy. *Curr Pharm Biotechnol* 12:2015–2019, 2011

32. Kielstein JT, David S: Pro:Renal replacement trauma or Paracelsus 2.0. *Nephrol Dial Transplant* 28:2728–2733, 2013

33. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 39(2):165–228, 2013

34. Mueller BA, Pasko DA, Sowinski KM: Higher renal replacement therapy dose delivery influences on drug therapy. *Artif Organs* 27(9):808–814, 2003