# Adding to the Armamentarium: Antibiotic Dosing in Extended Dialysis

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The dismal survival rates for critically ill patients with AKI have not improved much over the past few decades despite many advances in renal replacement therapies (RRTs). Some of the continued poor outcomes can be attributed to the fact that the demographics of patients treated in the intensive care unit (ICU) with RRTs have changed considerably (1,2). As pharmacists, perhaps the most personally disappointing aspect of the poor survival rates is that infection remains a leading cause of death in these patients (3). Although the emergence of multidrug-resistant organisms is a challenge to all clinicians (4,5), the fact remains that the high infectious death rate in critically ill patients with AKI is usually caused by bacteria and fungi that are sensitive to drugs on the existing hospital formulary. Timely broad-spectrum antibiotic dosing has been a mainstay of the Surviving Sepsis Guidelines (6); therefore, why should infection and shock continue to be the leading causes of death in critically ill patients with AKI? Adequacy of antibiotic therapy in these patients may be an important contributor to the problem.

In *CJASN*, the work by Lorenzen *et al.* (7) addresses dosing of ampicillin/sulbactam in a pharmacokinetic study in this patient population. More importantly, the work by Lorenzen *et al.* (7) links their pharmacokinetic findings to projected pharmacodynamic effects. These investigators measured ampicillin and sulbactam plasma concentrations achieved in critically ill patients receiving an extended dialysis (ED) treatment and then determined whether the plasma concentrations would yield bactericidal values that might result in infection cure.

The work of Craig (8) opened many people's eyes to the importance of applying pharmacodynamic principles identified from *in vitro* and animal models to antibiotic treatment in humans. Since that time, the value of these models in the determination of antibiotic doses in patients is well accepted (9). Unfortunately, these pharmacokinetic/pharmacodynamic-derived antibiotic dosing guidelines were not designed for septic patients with AKI receiving a myriad of RRTs that result in rapid removal of antibiotics (10). Therein may lie much of the answer to question of the high infectious mortality rate in this population.

When an antibiotic is brought to market, there is no mandate and certainly little incentive for the manufacturer to conduct pharmacokinetic trials in critically ill patients receiving RRTs (11). In the rare case that an RRT dosing recommendation is made in the antibiotic's package insert, invariably, the recommendation is for three times per week intermittent hemodialysis (IHD), which is the most common in the outpatient CKD environment. Even in institutions where IHD is the preferred form of RRT in the ICU, these recommendations are of limited value for two main reasons. First, drug clearance that is achievable in stable CKD patients with extant dialysis vascular access rarely can be achieved in hypotensive, critically ill patients with temporary vascular access. Consequently, the delivered IHD dose in AKI is much smaller than the prescribed hemodialysis dose (12). Second, the catabolic nature of sepsis patients and the relatively poor delivered dose of dialysis mean that IHD must be administered more often than three times per week (13). Therefore, drug dosing recommendations based on three times per week IHD do not work well in the ICU.

Hemodynamic instability, fluid overload, and increased metabolic needs of critically ill patients with AKI led to the development of new types of RRT. Continuous RRTs (CRRTs) are now used as frequently as IHD in ICUs worldwide (14). Antibiotic dosing in CRRT has been reviewed recently (15–18). The advantage of antibiotic dosing in CRRT is that drug removal is relatively constant, resulting in relatively predictable drug dosing. The work by Lorenzen *et al.* (7) studies a newer, hybrid form of RRT that uses a standard hemodialysis machine but a longer treatment time, thus allowing for less-aggressive solute and volume removal per unit time than standard IHD (19). However, these technical advantages may be outweighed by the challenges in antibiotic dosing using hybrid hemodialysis therapies like ED (20,21). With ED (and IHD), patients with AKI have impaired drug clearance for part of the day and potentially supraphysiologic clearance during the ED procedure. With two different clearance rates occurring each day, it is evident that **when** the dose is given in relation to ED may be a more important factor than **what** dose. In the study by Lorenzen *et al.* (7), ED is instituted 3 hours after the ampicillin/sulbactam 2/1-g infusion ended. The ED session removed >80% of the ampicillin/sulbactam dose. With these drug administration parameters and ED operating characteristics, Lorenzen *et al.* (7) correctly conclude that the pharmacodynamic target (time greater than minimum inhibitory concentration (MIC) of at least 50% of the dosing

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interval) for most pathogens would not be met. As the work by Lorenzen *et al.* (7) mentions, the problem is that the same ampicillin/sulbactam 2/1-g dose administered at a time other than the time studied would give considerably different pharmacokinetic and pharmacodynamic results. For example, if the same ampicillin/sulbactam dose is administered >3 hours before ED, less drug would be removed by ED, resulting in a longer time above MIC. This dosing regimen might meet the pharmacodynamic target of time greater than MIC. In contrast, if the ampicillin/sulbactam dose was infused immediately before ED, drug would be removed faster and pharmacodynamic targets would be missed by a greater margin. Consequently, ampicillin/sulbactam given too early or too late in relation to ED could result in supra- or subtherapeutic plasma concentrations. Clearly, dose timing could have an effect on patient outcome.

Three main stumbling blocks for antibiotic dosing with ED become apparent. The first, as outlined above, is that the clinician must be able to accurately predict the future by timing the antibiotic doses to when ED therapy will be initiated. In patients with severe critical illness, it can be challenging to predict when ED will begin. The present study suggests that ampicillin/sulbactam should be given 3 hours before ED (7). However, these same researchers recently studied daptomycin and a similar ED regimen, and they recommended that daptomycin administration should occur within 8 hours of ED (22). Gentamicin has been studied in ED, and the study suggested dosing immediately after ED (23). Interestingly, it might make more pharmacodynamic sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical standpoint, these different dose administration times in relation to ED can be difficult to schedule.

The second barrier for effectively dosing antibiotics in ED is that ED is performed differently at each institution. Variants of ED go by many different names (slow low-efficiency dialysis, sustained low-efficiency daily diafiltration, go-slow dialysis, prolonged intermittent renal replacement therapy, etc.) (19), and they use different dialyzer types, treatment durations, and blood/dialysate flow rates (25). Before applying the ampicillin/sulbactam recommendations from the present study, one must ensure that the same ED regimen is used in your institution (7). Finally, ED pharmacokinetic studies have been conducted for very few drugs. Letters to the editor have been published regarding ED experiences dosing the antifungal drugs anidulafungin (26) and voriconazole (27). The most recent ED antibiotic dosing review published in 2011 found that pharmacokinetic studies have only been conducted on daptomycin, ertapenem, gentamicin, levofloxacin, linezolid, meropenem, moxifloxacin, and vancomycin (28). Lorenzen *et al.* (7) are commended for publishing the pharmacokinetic results of the ninth antibacterial drug studied in ED, ampicillin/sulbactam. However, the choice of using ED in the ICU is inextricably linked to a limited therapeutic armamentarium of nine antibacterial and two antifungal agents that have been studied in this setting. This issue has led some to conclude that rational drug dosing in ED cannot be accomplished with such a paucity of pharmacokinetic data (29). Therapeutic drug monitoring (TDM) to ascertain whether pharmacokinetic and pharmacodynamic targets are being met is the obvious solution, but most sites worldwide do not have access to TDM for most of the antibiotics used in the ICU.

As more pharmacokinetic studies are conducted in patients with AKI in the ICU setting, we will find that the problem of appropriate antibiotic dosing is not simply a problem with ED. The fact is that existing drug dosing recommendations for more traditional RRTs, like IHD and CRRT, also need to focus on achieving pharmacodynamic targets to reach cure and reduce development of antimicrobial resistance (30). RRT technology has changed tremendously in the ICU (11). RRT dose delivery is higher in the ICU, which decreases antibiotic plasma concentrations. Indeed, the fact that the dialysis dosing trials did not account for higher antibiotic removal in the patients randomized to higher dialysis dose may account for the lack of clarity in the results of these trials (31).

Consequently, many of the antibiotic doses that seemed to be appropriate for patients receiving RRTs in the ICU in the past are probably insufficient today (32,33). Pharmacokinetic and pharmacodynamic studies like the one by Lorenzen *et al.* (7) need to continue to be conducted for all types RRT, to begin to reduce the infectious mortality rate in this vulnerable patient population.

### References
1. Esper AM, Martin GS: The impact of cormorbid conditions on critical illness. *Crit Care Med* 39: 2728–2735, 2011
2. Cartin-Ceba R, Kojicic M, Li G, Kor DJ, Poulose J, Herasevich V, Kashyap R, Trillo-Alvarez C, Cabello-Garza J, Hubmayr R, Seferian EG, Gajic O: Epidemiology of critical care syndromes, organ failures, and life-support interventions in a suburban US community. *Chest* 140: 1447–1455, 2011
3. Woodrow G, Turney JH: Cause of death in acute renal failure. *Nephrol Dial Transplant* 7: 230–234, 1992
4. Rogers BA, Aminzadeh Z, Hayashi Y, Paterson DL: Country-to-country transfer of patients and the risk of multi-resistant bacterial infection. *Clin Infect Dis* 53: 49–56, 2011
5. Rosenberger LH, Hranjec T, Politano AD, Swenson BR, Metzger R, Bonatti H, Sawyer RG: Effective cohorting and "super-isolation" in a single intensive care unit in response to an outbreak of diverse multi-drug-resistant organisms. *Surg Infect (Larchmt)* 12: 345–350, 2011
6. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 36: 296–327, 2008
7. Lorenzen JM, Broll M, Kaever V, Burhenne H, Hafer C, Clajus C, Knitsch W, Burkhardt O, Kielstein JT. Pharmacokinetics of ampicillin/sulbactam in critically ill patients with acute kidney injury undergoing extended dialysis. *Clin J Am Soc Nephrol* 7: 385–390, 2012
8. Craig WA: Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 26: 1–10, 1998

9. Ambrose PG, Bhavnani SM, Rubino CM, Louie AL, Gumbo T, Forrest A, Drusano GL: Pharmacokinetics-pharmacodynamics of antimicrobial therapy: It's not just for mice anymore. *Clin Infect Dis* 44: 79–86, 2007

10. Eyler RF, Mueller BA: Antibiotic pharmacokinetic and pharmacodynamic considerations in patients with kidney disease. *Adv Chronic Kidney Dis* 17: 392–403, 2010

11. Mueller BA, Smoyer WE: Challenges in developing evidence-based drug dosing guidelines for adults and children receiving renal replacement therapy. *Clin Pharmacol Ther* 86: 479–482, 2009

12. Evanson JA, Himmelfarb J, Wingard R, Knights S, Shyr Y, Schulman G, Ikizler TA, Hakim RM: Prescribed versus delivered dialysis in acute renal failure patients. *Am J Kidney Dis* 32: 731–738, 1998

13. Clark WR, Mueller BA, Kraus MA, Macias WL: Extracorporeal therapy requirements for patients with acute renal failure. *J Am Soc Nephrol* 8: 804–812, 1997

14. Bouchard J, Macedo E, Mehta RL: Dosing of renal replacement therapy in acute kidney injury: Lessons learned from clinical trials. *Am J Kidney Dis* 55: 570–579, 2010

15. Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J: Principles of antibacterial dosing in continuous renal replacement therapy. *Crit Care Med* 37: 2268–2282, 2009

16. Churchwell MD, Mueller BA: Drug dosing during continuous renal replacement therapy. *Semin Dial* 22: 185–188, 2009

17. Kuang D, Verbine A, Ronco C: Pharmacokinetics and antimicrobial dosing adjustment in critically ill patients during continuous renal replacement therapy. *Clin Nephrol* 67: 267–284, 2007

18. Heintz BH, Matzke GR, Dager WE: Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 29: 562–577, 2009

19. Mushatt DM, Mihm LB, Dreisbach AW, Simon EE: Antibiotic dosing in slow extended daily dialysis. *Clin Infect Dis* 49: 433–437, 2009

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

21. Decker BS, Mueller BA, Sowinski KM: Drug dosing considerations in alternative hemodialysis. *Adv Chronic Kidney Dis* 14: e17–e26, 2007

22. Kielstein JT, Eugbers C, Bode-Boeger SM, Martens-Lobenhoffer J, Haller H, Joukhadar C, Traunmüller F, Knitsch W, Hafer C, Burkhardt O: Dosing of daptomycin in intensive care unit patients with acute kidney injury undergoing extended dialysis—a pharmacokinetic study. *Nephrol Dial Transplant* 25: 1537–1541, 2010

23. Manley HJ, Bailie GR, McClaran ML, Bender WL: Gentamicin pharmacokinetics during slow daily home hemodialysis. *Kidney Int* 63: 1072–1078, 2003

24. Sowinski KM, Magner SJ, Lucksiri A, Scott MK, Hamburger RJ, Mueller BA: Influence of hemodialysis on gentamicin pharmacokinetics, removal during hemodialysis, and recommended dosing. *Clin J Am Soc Nephrol* 3: 355–361, 2008

25. Fliser D, Kielstein JT: Technology Insight: Treatment of renal failure in the intensive care unit with extended dialysis. *Nat Clin Pract Nephrol* 2: 32–39, 2006

26. Burkhardt O, Kaever V, Burhenne H, Kielstein JT: Extended daily dialysis does not affect the pharmacokinetics of anidulafungin. *Int J Antimicrob Agents* 34: 282–283, 2009

27. Burkhardt O, Thon S, Burhenne J, Welte T, Kielstein JT: Sulphobutylether-beta-cyclodextrin accumulation in critically ill patients with acute kidney injury treated with intravenous voriconazole under extended daily dialysis. *Int J Antimicrob Agents* 36: 93–94, 2010

28. Bogard KN, Peterson NT, Plumb TJ, Erwin MW, Fuller PD, Olsen KM: Antibiotic dosing during sustained low-efficiency dialysis: Special considerations in adult critically ill patients. *Crit Care Med* 39: 560–570, 2011

29. Roberts JA, Mehta RL, Lipman J: Sustained low efficiency dialysis allows rational renal replacement therapy, but does it allow rational drug dosing? *Crit Care Med* 39: 602–603, 2011

30. Roberts JA, Kruger P, Paterson DL, Lipman J: Antibiotic resistance—what's dosing got to do with it? *Crit Care Med* 36: 2433–2440, 2008

31. Kielstein JT: Dosage of renal replacement therapy in acute renal failure. *Dtsch Med Wochenschr* 134: 1697–1699, 2009

32. Seyler L, Cotton F, Taccone FS, De Backer D, Macours P, Vincent JL, Jacobs F: Recommended $\beta$-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. *Crit Care* 15: R137, 2011

33. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney B, Ungerer J, Lipman J, Roberts JA: Sub-therapeutic initial beta-lactam concentrations in select critically ill patients: Association between augmented renal clearance and low trough concentrations [published online before print December 22, 2011]. *Chest* doi:10.1378/chest.11-1671