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). Therewith 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 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...
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.

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References


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