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 therapy for patients receiving RRTs (11). In the rare case that an RRT procedure is not performed, 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
interval) for most pathogens would not be met. As the work by Lorenzen et al. (7) mentions, the problem is that the same ampicillin/sulfactam 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/sulfactam 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/sulfactam dose was infused immediately before ED, drug would be removed faster and pharmacodynamic targets would be missed by a greater margin. Consequently, ampicillin/sulfactam 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/sulfactam 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 sense to administer gentamicin immediately before 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 sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administer gentamicin immediately before ED, which has been suggested with IHD (24). From a practical sense to administ


Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Pharmacokinetics of Ampicillin/Sulbactam in Critically Ill Patients with Acute Kidney Injury undergoing Extended Dialysis,” on pages 385–390.