Antibiotic dosing during sustained low-efficiency dialysis: Special considerations in adult critically ill patients*

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Objective: **To address issues of antibiotic dosing during sustained low-efficiency dialysis by using available pharmacokinetic data, intermittent and continuous renal replacement therapy dialysis guidelines, and our experience with sustained low-efficiency dialysis.**

Data Resources: **Published clinical trials, case reports, and reviews of antibiotic dosing in humans during sustained low-efficiency dialysis.**

Data Extraction: **A search of electronic databases (MEDLINE, PubMed, and Ovid) was conducted by using key words of extended daily dialysis, sustained low-efficiency dialysis, antibiotics, antimicrobial agents, and pharmacokinetics. MEDLINE identified 32 sustained low-efficiency dialysis articles, and PubMed identified 33 articles. All papers describing antibiotic clearance prospectively in patients were considered for this article.**

Data Synthesis: **We identified nine original research articles and case reports that determined the impact of sustained low-efficiency dialysis on antibiotic clearance in patients. The blood and dialysate flow rates, duration of dialysis, type of filter, and the pharmacokinetic parameters were extracted from each article. If multiple articles on the same drug were published, they were compared for consistency with the aforementioned dialysis parameters and then compared with forms of continuous renal replacement therapy. Antibiotic clearance by sustained low-efficiency dialysis was determined to be similar or higher than continuous renal replacement therapy therapies. The estimated creatinine clearance during sustained low-efficiency dialysis was approximately 60 mL/min to 100 mL/min depending on the blood and dialysate flow rates and the type of filter used.**

Conclusions: **The potential for significant drug removal during an 8-hr-or-longer sustained low-efficiency dialysis session is evident by the limited number of studies available. Because significant amounts of drug may be removed by sustained low-efficiency dialysis combined with altered pharmacokinetic variables in critically ill patients, the risk for suboptimal drug concentrations and pharmacodynamics must be considered. Appropriate dose and calculation of dosing intervals is essential to provide adequate antibiotic therapy in these patients. It is recommended that institutions who utilize sustained low-efficiency dialysis establish dosing guidelines for all pharmacists and physicians to follow to provide consistent delivery of antibiotics at adequate concentrations. (Crit Care Med 2011; 39:560–570)**

Key Words: pharmacokinetics; dialysis; antibiotics; anti-infectives; sustained low-efficiency dialysis; continuous renal replacement therapy; critical care

Critically ill patients demonstrate alterations in drug pharmacokinetics due to multiorgan dysfunction syndrome, acute changes in volume status (both intra- and extravascular), and alterations in metabolism, absorption, and elimination. Chief among these alterations is the development of acute kidney injury often leading to an increased rate of morbidity and mortality. The incidence of acute kidney injury in critically ill patients has been estimated at 1% to 25% of admissions with a resulting mortality ranging from 28% to 90% (1, 2). In an attempt to reduce refractory fluid overload and metabolic acidosis and the associated morbidity and mortality of acute kidney injury, both intermittent and continuous renal replacement therapies (CRRTs) have been utilized.

Continuous renal replacement therapies are not new to the intensive care unit (ICU) as they have been used for >25 yrs (3, 4). Continuous therapies are preferred among critically ill patients who are hemodynamically unstable. In addition, CRRT is preferred over intermittent hemodialysis (IHD) techniques due to improved efficacy in severely catabolic patients (5). Despite these advantages, morbidity and mortality remain high, and better dialysis techniques have been sought. Marshall et al (5) first described sustained low-efficiency dialysis (SLED), a hybrid dialysis modality that utilizes IHD equipment in conjunction with reduced blood and dialysate flow rates. SLED offers several advantages over conventional CRRT, including higher solute clearance and decreased supply costs. When first introduced, SLED was utilized for periods of 6–12 hrs. However, at our institution and others, SLED is being utilized as a continuous therapy (6). Despite the adoption of SLED by some nephrologists as the dialysis modality of choice in hemodynamically unstable patients, little is known regarding the effect of SLED on drug clearance.

Few studies have examined the pharmacokinetics and resulting pharmacodynamics of drug therapy during CRRT, and even fewer have evaluated the impact of

*See also p. 602.

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Table 1. A comparison of different methods of dialysis

Parameter	Intermittent Hemodialysis	Continuous Venovenous Hemodialysis	Sustained Low-Efficiency Dialysis
Duration	3–4 hrs	Days	8 hrs to days
Dialysate flow (mL/min)	500–800	16–32	100–300
Blood flow (mL/min)	300–500	100–200	160–200
Urea clearance (mL/min)	150–250	20–25	70–80
Hemofiltration	Not used in the United States	Yes	Yes
Hemofiltration flow rates	Not applicable	20–40 mL/kg/hr	100 mL/min

References 6, 15, 18, 67, and 68.

SLED on drug removal (7–9). Most early drug pharmacokinetic studies with CRRT utilized low hemofiltration rates and dialysate flows, which provide little information in critically ill patients who receive much higher hemofiltration and flow rates. Although SLED uses lower flow rates than IHD, the duration of SLED often results in higher clearance rates, and thus has a potentially greater impact on drug clearance. The goals of antibiotic dosing are to maximize the pharmacodynamic effect while limiting drug-associated toxicity. This is especially true among critically ill patients who already have significant alterations in pharmacokinetic and pharmacodynamic relationships associated with underlying disease processes, before the introduction of dialysis to their treatment regimen (10, 11). The primary objectives of this review paper are to provide a greater understanding of SLED and the differences from CRRT, to critically review the available literature on antibiotic pharmacokinetics during SLED, and to share our experiences, interpretations, and recommendations for antibiotic dosing during SLED.

METHODS

To identify relevant articles, a search of electronic databases was conducted (PubMed, MEDLINE, and Ovid) from January 1950 to May 2010. Search results were limited to English-language articles only. The following key words were used: extended daily dialysis, SLED, slow low-efficiency dialysis, antibiotics, antibacterial agents, and pharmacokinetics. Articles were assessed for relevance by a single investigator. Excluded articles failed to address drug dosing, kinetics, or solute removal. Ovid did not identify any additional papers. Included articles were reviewed and information regarding dialysis specifications, drug dosing and elimination, pharmacokinetics, and patient characteristics were extracted.

RESULTS

The MEDLINE search yielded the following results: Extended daily dialysis provided 26 articles, SLED yielded 32 articles, and slow low-efficiency dialysis supplied two articles. The PubMed search provided slightly different numbers of results: Extended daily dialysis yielded 51 articles, SLED provided 33 articles, and slow low-efficiency dialysis supplied 16 articles. When the dialysis search terms were combined with the terms antibiotics or antibacterial agents, nine relevant results were obtained. Those results are summarized in a later section.

SLED

IHD is currently the standard of care for the treatment of both acute and chronic renal failure (12). IHD utilizes high blood and dialysate flow rates to remove large quantities of toxins or drugs over a short period of time, usually between 3 and 4 hrs. Blood flow rates are set at 300–500 mL/min, and dialysate flow rates are set at 500–800 mL/min. Due to large fluid shifts in a short duration of time, session lengths can be extended and blood rates reduced if standard IHD causes hemodynamic instability.

In comparison, CRRTs operate in a continuous mode and are only interrupted for clotted circuits, patient procedures, and routine dialysis circuit changes whereas IHD treatments typically last 3–4 hrs. These CRRT therapies involve either diffusive or convective clearance and use similar mechanisms as in IHD. However, by using a slower rate of fluid or solute removal, they are considered to be better tolerated. Different CRRT modalities utilize hemofiltration, hemodialysis, or a combination of the two (hemodiafiltration) for solute removal. Diffusion is the movement of solutes from a higher concentration to a lower concentration across the semipermeable dialysis membrane and is the primary mechanism to remove metabolic waste. Convective clearance occurs as solutes are dragged across the semipermeable dialysis membrane during ultrafiltration. The method of hemofiltration utilizes large volumes of dilutional fluid and high ultrafiltration rates to remove solute.

SLED is a hybrid dialysis modality in which conventional dialysis equipment is used with the reduced blood and dialysate flow design of CRRT. It was first utilized in the United States at the University of Arkansas for Medical Sciences in 1998 and was designed to provide adequate solute control and better hemodynamic stability with low cost and ease of use for nursing personnel (5). Although some institutions utilize SLED as a continuous modality, it was originally designed to run overnight (8–12 hrs), thus providing better access to the patient for procedures during the day. Blood flow and dialysate flow rates are generally set between 100 and 300 mL/min. These flow rates are much lower than those utilized for IHD. The blood flow rate is similar to those used for continuous venovenous hemodialysis (CVVHD), whereas the dialysate flow falls in between. These dialysis methods are compared in Table 1. Like IHD, drug removal is achieved primarily through diffusion, thus favoring the removal of waste products and solutes with low molecular weights (13). However, if hemofiltration is added solutes may be transported via convection as well, which would allow molecules of greater molecular weights to be removed (13). Therefore, an important consideration for drug dosing during SLED is the type of dialysis and whether hemofiltration is employed.

Comparison of Dialysis Modalities

In comparison with traditional IHD, SLED provides similar or better solute removal while minimizing the hemodynamic instability that often results from short-term, large fluid shifts (14). Although it utilizes the same equipment as conventional dialysis, SLED does have some additional requirements. First, although SLED can be run on the conventional dialysis machine without additional software, some recalibration of temperature settings is required. There

Table 2. Review of published pharmacokinetic studies and case reports with antimicrobial agents during sustained low-efficiency dialysis

Drug	Study Design	Patients	SLED Duration (hr)	Qd (mL/min)	Qb (mL/min)
Anidulafungin (66)	Single–dose pharmacokinetic	1	8	180	180
Daptomycin (25)	Single-dose pharmacokinetic	1	12	100	200
Daptomycin (26)	Single-dose pharmacokinetic	10	8	160	160
Gentamicin (38)	Prospective, single-dose pharmacokinetic Home dialysis patients	8	8	300	200
Gentamicin (32)	Single- and multidose pharmacokinetic, Monte Carlo simulation Critically ill patients	14	6 (designed for 10 hrs)	300	300
Ertapenem (51)	Prospective, single-dose pharmacokinetic	6	8	160	160
Meropenem (47)	Prospective, single-dose pharmacokinetic	10	8	160	160
Vancomycin (47)	Prospective, single-dose pharmacokinetic	10	8	160	160
Vancomycin (48)	Prospective, single-dose pharmacokinetic	11	24	100	200
Linezolid (58)	Prospective, single-dose pharmacokinetic	5	8-9	100	200
Moxifloxacin (61)	Prospective pharmacokinetic	15	8	160	160
Levofloxacin (61)	Prospective pharmacokinetic	15	8	160	160

SLED, sustained low-efficiency dialysis; Qd, dialysate flow; Qb, blood flow; IHD, intermittent dialysis; Cl, clearance; Vd, volume of distribution; PK, pharmacokinetics.

are now software programs available that provide a continuous mode that eliminates the necessity of recalibration (5). Second, as the blood and dialysate flow rates are slower with SLED than with IHD, the extracorporeal circuitry is at an increased risk of clotting during the dialysis session. Therefore, anticoagulation with systemic heparinization or citrate regional anticoagulation is often required to minimize this risk (5). Either method is effective at reducing the risk of clotting in the dialysis circuit, but both carry some inherent risk for adverse effects.

In comparison to other CRRT modalities, SLED provides some distinct advantages. It does not require specialized equipment, does not require the same level of manpower to operate, and does not require specialized dialysate solutions (15, 16). In addition, due to its higher dialysate flows relative to CVVHD, it may provide a higher drug and solute clearance rate (17). Despite these differences between techniques, no one dialysis modality has been proven superior to the others in terms of patient mortality (5).

Antibiotic Clearance and Dosing During SLED

When evaluating published literature for drug clearance in SLED, one must be cognizant of the specific settings or protocol used for the procedure. The principles of antimicrobial drug dosing in CRRT have recently been discussed in detail in this journal (10). However, some basic principles will be reviewed here. Like CVVHD and IHD, the most important factor determining drug removal is the degree of protein binding. Operating characteristics vary considerably and can greatly affect the drug removal. As shown in Table 2, review of the available studies on SLED drug clearance indicate blood flows vary from 160 to 200 mL/min, and dialysate flows vary from 100 to 300 mL/min. Unlike CVVHD where low dialysate flows limit solute removal, the higher dialysate flow rates used in SLED markedly increase urea clearance rates. Whereas typical CVVHD urea clearance rates are 20–35 mL/min, urea and creatinine clearances have recently been measured at 76 and 75 mL/min, respectively, using continuous SLED with a blood flow of 200 mL/min and dialysis flow of 100 mL/min (18, 19).

A variety of dialyzers have been used for SLED (Table 2). With the exception of one vancomycin investigation, studies have utilized high-flux polysulfone membranes with surface areas between 0.8 and 1.6 m^2 (Table 2). However, the influence of filter surface area on drug clearance is diminished at the low blood and dialysate flow rates used in SLED. In addition, membrane flux can have a significant impact on middle molecular weight drugs of 500 to 5000 Da (e.g., antibiotics) while high molecular weight drugs (>5000 Da) are not effectively removed by low-flux or high-flux dialysis membranes (20). High-flux membranes readily remove non-protein–bound drug by diffusion, and drug clearance correlates with urea clearance (19, 21). Hence, when evaluating drug clearance studies in patients undergoing SLED, it is important to not only assess the blood and dialysate flow rates, but also the dialyzer membrane surface area and flux.

Table 2. Review of published pharmacokinetic studies and case reports with antimicrobial agents during sustained low-efficiency dialysis

Filter Type	Outcomes	Study Dosing Recommendations
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	PK data comparable to healthy adults	No dosage adjustment necessary
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	PK data indicates SLED effectively eliminated daptomycin to a larger extent than IHD	Dosing interval every 48 hrs as recommended in IHD may results in under-dosing
Fresenius F50S polysulfone; high-flux surface areas 1.3 m^2	Cl 63 ± 9 mL/min with a mean drug cleared by one dialysis treatment of 23.3%	6 mg/kg daily to prevent under dosing
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	PK data indicates SLED cleared 70% of gentamicin dose, with significantly shorter drug half-life during SLED sessions	2-2.5 mg/kg ABW after each SLED session to provide peak approximately 7.5 μg/mL and trough approximately 0.7 μg/mL
Fresenius F60S polysulfone; high-flux surface areas 0.6 m^2	PK data indicated rapid Cl by SLED (13.6 hrs half-life)	Gentamicin 6 mg/kg lean body weight every 48 hrs following a 30-min infusion and given 1 hr before SLED
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	Total Cl on dialysis was comparable to controls with normal renal function not requiring renal replacement therapy with no difference in Vd[1]	Intensive care unit patients undergoing SLED should not receive reduced doses to ensure optimal drug concentrations
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	Significant removal by high-flux SLED	Current IHD dosage adjustments for meropenem may result in serious underdosing; exact doses must be tailored to illness severity, bacterial minimum inhibitory concentration, and drug levels
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	Significant removal by high-flux SLED	Vancomycin concentrations reach subtherapeutic at approximately 30 hrs
Fresenius F4 and F5; polysulfone; low-flux surface area 0.8 and 1.0 m^2	Similar removal as seen with other continuous renal replacement therapy modalities	Recommend obtaining a random vancomycin level 24 hrs after infusion
Fresenius F7HPS polysulfone; low-flux surface area 1.6 m^2	Significant drug removal by SLED	Doses should be administered after SLED sessions when possible
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	Increased Cl by SLED	Moxifloxacin requires a standard dose after SLED session
Fresenius F60S polysulfone; high-flux surface areas 1.3 m^2	Increased Cl by SLED	Levofloxacin may require a dose adjustment after SLED session

Antibiotics that require dose adjustment for SLED share some common properties. In general, antibiotics that have increased clearance by SLED are those that have low protein binding, small molecular size, high water solubility, or high dependence on renal clearance. These agents often require adjusting the timing of administration or supplementing the usual dose after IHD. It would follow that SLED patients may also require adjusted dosing. The various antibiotic agents in each class often share similar pharmacokinetic properties, and therefore, dosing recommendations for SLED patients can be based on available study data. However, there are subtle differences between certain agents in antibiotic classes that may lead to differences in clearance, making the continued study of pharmacokinetics in these patients essential to providing the best outcomes in the critically ill populations. Many antibiotics require loading doses to assure adequate initial concentrations; however, none of the published articles with SLED utilized them. We recommend the use of sound clinical judgment for each patient and applying loading doses in a similar manner as recommend for CRRT (11).

Providing adequate concentrations of antibiotics to the site of infection is crucial to the successful treatment and positive outcomes of all patients, especially those residing in an ICU. Antibiotic pharmacodynamic parameters are easily altered in the ICU population not only by the underlying disease, but also by acute physiologic changes resulting from severe infections. SLED may significantly increase antibiotic clearance and alter pharmacodynamic parameters resulting in diminished bacterial eradication and clinical response rates. In Table 2, all published studies and case reports of antibiotic pharmacokinetics during SLED are summarized. The following discussion not only addresses these studies in greater detail, but also addresses other agents in the same antibiotic class and provides dosing recommendations based on the current understanding of SLED. For the purpose of consistency in this review, the term "extended daily dialysis" is replaced by SLED. Blood and dialysate flow rates and the use of low- and high-flux membranes differ from one report to the next and therefore, the dosing recommendations in this review must be tailored to the dialysis parameters used in individual institutions.

Daptomycin. Daptomycin, a lipopeptide antibiotic, has a relatively long half-life of 8–9 hrs, is primarily eliminated in the urine (78%; 50% as unchanged), has a small volume of distribution (0.1 L/kg), and is highly protein bound at 92%, which suggests the drug remains within plasma and interstitial fluid (22). At least one report indicates daptomycin is more bioavailable than the high protein binding would imply (22). Predicting daptomycin clearance during dialysis is difficult with a low volume of distribution suggesting significant clearance, but the high protein binding suggests otherwise. However, the plasma protein binding is weak, and critically ill patients often have decreased plasma proteins, which indicate a significant clearance by dialysis would be expected.

Limited data are available regarding the impact of hemodialysis on daptomycin clearance. Dvorchik et al (23) de-

scribed the disposition and clearance from a group of subjects with varied renal function by creatinine clearance (Cl_{cr} >80 mL/min to <30 mL/min) and a group with end-stage renal disease receiving either IHD or continuous ambulatory peritoneal dialysis. IHD had a modest impact on daptomycin with 15% of drug removed over a 4-hr session, prompting the investigators to recommend dosing after dialysis without additional supplemental doses (23). Limited data are available describing the impact of CRRT on daptomycin clearance. An *in vitro* study evaluated the impact of continuous venovenous hemofiltration (CVVH) on daptomycin clearance in a simulated dialysis model (24). CVVH clearance of daptomycin from whole blood exceeded the physiologic clearance described in patients with normal renal function. A review of antibiotic dosing in patients receiving CRRT contradicted these findings by recommending daptomycin dosing of 4–6 mg/kg every 48 hrs in patients receiving CVVH, CVVHD, or continuous venovenous hemodiafiltration (CVVHDF) (11). Based on the extensive clearance, the authors recommended daptomycin blood concentrations be monitored in patients receiving CRRT (24).

Two studies have determined the effect of SLED on daptomycin clearance (Table 2) (25, 26). A 67-yr-old male (110 kg total body weight; albumin 2.1 g/dL) with infective endocarditis was treated with daptomycin 6 mg/kg infused over 30 mins. He received SLED over a 12-hr period, with a dialysate flow rate of 100 mL/min and a blood flow rate of 200 mL/min by using a high-flux polysulfone dialyzer (F60S, surface area 1.3 m^2). A single blood sample was obtained before dosing, and serial blood samples were obtained after a daptomycin dose with an additional sample of the total dialysate obtained to calculate the absolute amount of drug removed. The authors compared this case study with a previous paper in which patients received daptomycin followed by IHD (27). The daptomycin clearance over a 12-hr SLED session was substantially higher compared with IHD with a calculated half-life of 9.4 hrs vs. 29.32 hrs, respectively (27). The data from the single case report suggest that SLED eliminates daptomycin effectively and to a larger extent than IHD. A recent study evaluated ten critically ill patients (mean Acute Physiology Assessment and Chronic Health Evaluation II score 35) with vancomycin-resistant enterococci endocarditis and bacteremia treated with daptomycin 6 mg/kg and receiving SLED with a high-flux polysulfone dialyzer (F60S; surface area 1.3 m^2) (26). A prospective single-dose pharmacokinetic study was completed with blood and dialysis flow rates of 160 mL/min with a dialysis time of 480 mins. The dialyzer clearance of daptomycin was 63 ± 9 mL/min with a mean amount of drug cleared by one dialysis treatment of 23.3%. Thus, the authors of both studies concluded that dosing daptomycin every 48 hrs as recommended with IHD would result in significant under dosing and suggested a more frequent dosing interval. Following the 8-hr SLED session, Kielstein et al (26) recommend a daily daptomycin dose of 6 mg/kg to prevent under dosing. We suggest a schedule that allows daptomycin be dosed daily at standard doses on the days a patient receives SLED, which should account for the observed increased clearance. We also suggest the daptomycin dose be adjusted to the patient's renal function on nondialysis days. Increased monitoring for adverse events and creatinine phosphokinase levels may be warranted and discontinuation of daptomycin should be considered if elevations occur.

Aminoglycosides. All aminoglycosides (amikacin, gentamicin, and tobramycin) are small hydrophilic molecules, and in non-ICU patients have short half-lives (mean 2.7 hrs), low protein binding (<30%), and a low volume of distribution (mean 0.25 L/kg) and are highly dependent upon renal clearance (half-life normal 2–3 hrs vs. renal failure 50–70 hrs) (28, 29). It is these same properties that predict aminoglycoside removal during IHD, CVVH, and SLED.

IHD provides an effective mechanism for removal of aminoglycosides in acute renal injury. Some authors have recommended a loading dose of 2–3 mg/kg for gentamicin and tobramycin and a 10-mg/kg loading dose for amikacin due to the alterations in volume of distribution in the critically ill (10, 11, 30). However, based on the current pharmacokinetic data, a greater understanding of aminoglycoside pharmacodynamics, and changes in bacterial susceptibility, it is unlikely that these loading doses will provide adequate treatment to maximize efficacy. To maximize aminoglycoside bacterial killing, a ratio of the peak serum concentration or the total area under-the-serum-concentration-time curve from 0 to 24 hrs (AUC_{0-24}) to the minimum inhibitory concentration (MIC) of the pathogen should equal or exceed 10 (peak serum concentration/MIC) and 70 to 120 (AUC_{0-24}/MIC) (31). The volume of distribution is significantly altered among critically ill patients with mean values ranging from 0.36 to 0.668 L/kg (32–37). The clinical impact of an increased volume of distribution is that the initial dose must be increased or inadequate pharmacodynamic ratios will be observed. To achieve these aforementioned pharmacodynamic ratios, some clinicians have suggested initial loading doses of 5–7 mg/kg for gentamicin or tobramycin (32, 33). Extrapolation of these recommendations from gentamicin/tobramycin to amikacin would result in a 15- to 20-mg/kg initial dose (32, 33, 36). All aminoglycoside maintenance dose recommendations are dependent upon serum concentration values and pre- or postdialysis timing of the serum level.

CVVH, CVVHD, and CVVHDF (CRRTs) also effectively clear aminoglycosides, and their continuous nature may provide accelerated drug removal (11). Loading doses are recommended for all aminoglycosides if a patient is receiving CRRTs. An initial one-time dose of 2–3 mg/kg for gentamicin and tobramycin or 10 mg/kg for amikacin should help to provide adequate serum concentrations (10, 11). As with IHD, these loading doses are unlikely to achieve adequate pharmacodynamic ratios to maximize efficacy against targeted pathogens and may need to be increased depending on the infection type.

Maintenance dosing in IHD is determined by drug clearance over the dosage interval (10, 30). Usual maintenance dose recommendations for gentamicin and tobramycin are 1–2.5 mg/kg every 48–72 hrs depending on indication, with the higher doses recommended for systemic Gram-negative infections (10, 11). Amikacin dosing usually ranges from 5 to 7.5 mg/kg every 48–72 hrs for IHD patients, again depending on indication (10, 11). Maintenance dosing in CRRT tends to be at shorter intervals relative to IHD, although it remains dependent on serum concentrations. In general, gentamicin and tobramycin may be dosed at 1–2.5 mg/kg every 24–48 hrs, whereas amikacin may be dosed at 7.5 mg/kg every 24–48 hrs during CRRT (10, 11). These dosing recommendations assume a CRRT dialysate rate of 1–2 L/hr and may require adjustment to be more aggressive should the ultrafiltration rate be higher.

SLED dosing is not well determined for aminoglycosides. Gentamicin was evaluated in a single-dose study involving eight non-critically ill patients receiving 8-hr home hemodialysis (Table 2) (38). Patients received a gentamicin dose of 0.6 mg/kg actual body weight, infused over 30 mins after an 8-hr session of SLED. Blood and dialysate flow rates were set at 200 mL/min and 300 mL/min, respectively, and a high-flux polysulfone dialysis filter was used (F50S; surface area 0.8 m^2). Based on the data analysis, a pharmacokinetic model was generated, which indicated approximately 70% of the gentamicin dose was removed during SLED. The elimination half-life of gentamicin was significantly different during SLED (3.7 ± 0.8 hrs) vs. between SLED sessions (20.4 ± 4.7 hrs). The authors also noted a lack of gentamicin concentration rebound after SLED stopped. This is a key difference between SLED and IHD gentamicin pharmacokinetics. In IHD, the removal rate of gentamicin is faster than the rate at which gentamicin is released from the tissues. However, due to the slower blood and dialysate flow rates in SLED, the gentamicin release rate is similar to the overall SLED removal rate. Therefore, because the tissue concentrations and serum concentrations during SLED are estimated to be at approximate equilibrium, there is little re-equilibration observed after the SLED session (31). The authors felt this difference may cause inappropriate evaluation of gentamicin levels after SLED, leading to potential dosing problems. Based on the findings from the pharmacokinetic model, the authors recommend a gentamicin dose of 2–2.5 mg/kg actual body weight after each 8-hr SLED session to provide an estimated peak level of 7.5 μg/mL and an estimated trough level of 0.7 μg/mL.

The effect of SLED on gentamicin pharmacokinetics was also evaluated in a prospective pharmacokinetic trial in critically ill patients with acute kidney injury (32). Data were collected from 28 gentamicin doses in 14 critically ill patients receiving a targeted SLED session of 10 hrs with a high-flux polysulfone dialyzer (F60S; surface area 0.6 m^2) with blood and dialysate flow rates of 300 mL/min, with a predilution rate of 50 mL/min. Following serial plasma collection for gentamicin concentration determination, a population pharmacokinetic model was used to describe gentamicin pharmacokinetics, and a Monte Carlo simulation was performed with doses between 3 mg/kg of body weight and 7 mg/kg (lean body weight; 70-kg patient normalized to 55 kg). The Monte Carlo simulation was used to determine the percentage of doses that would achieve the targeted pharmacodynamic parameter. The patients had a mean age of 66 yrs, were predominately male, weighed a mean 92.5 kg, and had a mean Acute Physiology Assessment and Chronic Health Evaluation III score of 98. A two-compartment pharmacokinetic model best described gentamicin with a half-life of 13.8 hrs during SLED and 153.4 hrs without SLED. The Monte Carlo analysis indicated a dose of 6 mg/kg (lean body weight) every 48 hrs as a 30-min infusion 1 hr before SLED resulted in 100% of targeted (70–120) AUC_{0-24}/MIC ratios. An interval of 48 hrs was required to allow trough concentrations to approach 1.5 mg/liter. The authors concluded that gentamicin should be administered at doses of 6 mg/kg lean body weight every 48 hrs with appropriate therapeutic monitoring to guide and optimize subsequent doses (32). Due to the similar pharmacokinetics for tobramycin, the same dosing recommendations could be utilized. Although no studies have been conducted in SLED with amikacin, extrapolating the gentamicin data to amikacin, a dose of 15–20 mg/kg lean body weight every 48 hrs could be considered.

Following the initial loading dose for patients on continuous SLED, it may be appropriate to consider a scheduled aminoglycoside regimen due to more extensive SLED clearance. Importantly, serum concentration monitoring should guide dosing adjustments. In addition, obese patients require an adjusted body weight based dose as actual body weight may lead to overdosing (11, 32).

Vancomycin. Vancomycin is a large molecule, but generally is well distributed into most body tissues (39–41). The volume of distribution is between 0.62 L/kg and 0.8 L/kg, and is 55% protein bound in patients without renal dysfunction or low albumin concentrations. In patients with severe renal dysfunction, the amount of protein binding is reduced approaching values of 18% to 20%. Vancomycin is primarily renally eliminated, with >80% removed through glomerular filtration, which results in a mean half-life of 6 hrs in subjects with normal renal function compared with >168 hrs in anephric patients. Due to significant renal elimination, vancomycin requires careful pharmacokinetic monitoring in patients with renal dysfunction (40). Dosing recommendations in patients with normal renal function typically range from 15 to 20 mg/kg every 8–12 hrs depending on indication and body weight. Recent guideline recommendations suggest more vigilant monitoring of vancomycin concentrations may be required to prevent treatment failures (40, 41). Several factors affect the clearance of vancomycin including the hemodialysis filter type and residual renal function (42). Vancomycin is poorly removed by low-flux membranes, whereas high-flux membranes significantly remove the drug by 30% to 50% (11, 43). Most dosing regimens follow the principle of administering a loading dose of 15–20 mg/kg postdialysis session on day 1 of therapy, followed by 500- to 1000-mg doses after subsequent dialysis sessions depending on predialysis vancomycin concentrations (1, 43). For example, Pai and Pai (44) recommend holding the dose of vancomycin for a predialysis concentration >20 μg/mL, administering 500 mg for concentrations between 5–20 μg/mL, and administering 1000 mg if the vancomycin concentration falls below 5 μg/mL.

CRRTs effectively remove vancomycin (30). Clearance by CRRT methods range from 11.5 to 19.3 L/day (39). Similar to HD, a vancomycin-loading dose of 15–20 mg/kg is recommended. Vancomycin maintenance dosing regimens may range from 500 mg intravenously (IV) every 12 hrs for CVVHDF to 10–15 mg/kg IV every 24–48 hrs for CVVH and CVVHD (42, 45, 46). Specifically, CVVHDF removes vancomycin to a greater degree than other CRRT methods (45).

Two pharmacokinetic studies have been published evaluating vancomycin clearance during extended daily dialysis (Table 2) (47, 48). Kielstein et al (47) evaluated ten critically ill patients with acute renal failure receiving vancomycin therapy. Vancomycin (1 g) was administered 12 hrs before SLED was initiated to obtain pharmacokinetic parameters both on and off SLED (40). SLED sessions lasted approximately 8 hrs and were performed with high-flux polysulfone dialyzers (F60S; surface area 1.3 m^2) with blood and dialysate flow rates of 160 mL/min. After administration of IV vancomycin, blood samples were drawn at several intervals throughout SLED. Dialysate samples were also collected to evaluate for total drug removal. Half-life and volume of distribution of vancomycin were 11.2 hrs and 0.57 L/kg, respectively, during

SLED, in comparison to a half-life of 37.3 hrs while off SLED. Drug removal by one 8-hr SLED session was estimated to be between 8% and 26%. Concentrations reached values of <10 μg/mL at 30 hrs after dose. The investigators of this study recommended administering a 20- to 25-mg/kg initial dose and obtaining drug levels no sooner than 12 hrs after dose to guide further therapy (47).

A second study evaluated the pharmacokinetics of vancomycin during a 24-hr session of SLED (48). SLED therapy was performed by using a low-flux filter (F4 and F5; 0.8 and 1.0 m^2) with blood and dialysate flow rates of 200 mL/min and 100 mL/min, respectively. Patients received vancomycin 15 mg/kg, based on actual body weight, as a single dose either before SLED or during SLED. Blood levels were drawn at 6, 12, and 24 hrs after drug infusion. If levels at 24 hrs were < 20 μg/mL, then vancomycin was redosed at 15 mg/kg. The volume of distribution of vancomycin in these patients ranged from 0.58 to 1.24 L/kg, with a mean of 0.84 L/kg. The half-life of vancomycin ranged from 18.8 to 96 hrs, with a mean of 43.1 hrs. The authors attributed the half-life variability to the volume of distribution differences in these patients. Of note, the investigators did not find that residual renal function had any effect on the half-life of vancomycin. The investigators recommended a vancomycin level 24 hrs after infusion due to the variability in half-life and inability to predict which patients require more frequent dosing.

SLED sessions of 12–24 hrs by using high-flux membranes would potentially require redosing more frequently than every 24 hrs. We recommend that a random vancomycin level be obtained between 12 hrs and 18 hrs after infusion during longer SLED sessions utilizing high-flux membranes to ensure concentrations do not fall below 10–20 μg/mL at any point during dialysis therapy.

Carbapenems. Carbapenems are only administered IV and are widely distributed into most bodily fluids, including the cerebral spinal fluid (49). Clearance during SLED has only been assessed for ertapenem and meropenem. The individual pharmacokinetics parameters of ertapenem and meropenem are substantially different. Meropenem has limited protein binding of approximately 2% whereas ertapenem is highly protein bound ranging from 90% to 95%. The half-lives for meropenem and ertapenem are 1 hr and 4 hrs, respectively. Both drugs exhibit extensive renal elimination. Meropenem is metabolized into a single active metabolite, with 70% of the drug excreted unchanged into the urine, and ertapenem is 80% renally excreted with 38% excreted unchanged. Doripenem and imipenem share a similar pharmacokinetic profile with meropenem with respect to half-life, renal elimination and protein binding. All carbapenems except ertapenem require dosage adjustment for renal impairment (Cl_{cr} <50 mL/min) and are extensively removed by IHD (11, 50). Despite the high protein binding of ertapenem, 30% of the drug is cleared in patients with end-stage renal disease receiving hemodialysis necessitating a supplemental dose following dialysis (51). Following IHD, an imipenem dose of 250–500 mg every 12 hrs and meropenem and doripenem dose of 500 mg every 24 hrs are recommended. All CRRTs increase carbapenem clearance beyond IHD with normal doses given for imipenem every 8 hrs and every 8–12 hrs for doripenem and meropenem (11).

Meropenem clearance during SLED has been evaluated in a single pharmacokinetic study of ten patients (Table 2) (47). One gram of meropenem was infused over 30 mins, 6 hrs before the initiation of SLED. A high-flux polysulfone filter (F60S; surface area 1.3 m^2) was used with blood and dialysate flow rates of 160 mL/min. Blood samples were drawn at the start of infusion, 0.5, 1, 2, 4, and 6 hrs after the administration of meropenem; before SLED started; during SLED at 2, 4, and 6 hrs; at the completion of the 8-hr SLED session, and 0.5, 1, 3, and 8 hrs after SLED completion. The half-life of meropenem during SLED was similar to the half-life of the drug on IHD as compared with a longer half-life during CVVH. Although the results were variable, up to 51% of meropenem was removed by SLED over the 8 hrs. Thus, a more aggressive dosing regimen of 500-1000 mg IV every 8 hrs is recommended in patients receiving high-flux SLED.

Ertapenem was also evaluated in a SLED pharmacokinetic study (Table 2) (51). Six patients undergoing SLED for 8 hrs with a high-flux polysulfone dialyzer (surface area 1.3 m^2), with blood and dialysate flow rates of 160 mL/min, received 1000 mg of ertapenem IV as a single dose. Blood samples were obtained at various time points before and after ertapenem administration. Due to high protein binding, the investigators evaluated both total and free ertapenem concentrations. Ertapenem-free concentrations were then evaluated in relation to MIC_{90} data for several common pathogens. The investigators concluded that 1000 mg of ertapenem daily results in sufficient concentrations above the MIC_{90} for most common pathogens for the entire dosing interval. Based on the half-life and MIC data provided by Burkhardt et al (51), we conclude that with high-flux SLED equal to or >8 hrs duration, once daily dosing of ertapenem should be sufficient to maintain adequate concentrations.

The clearances of doripenem and imipenem have not been evaluated in patients during SLED. However, based on their pharmacokinetic similarities to meropenem, we suggest utilizing a more aggressive dosing strategy than currently recommended for IHD during high-flux SLED. Imipenem doses of 500 mg IV every 6 hrs in patients >70 kg and doripenem doses of 500 mg IV every 8 hrs may be required to ensure adequate serum drug concentrations. Further data are needed to confirm these recommendations.

Linezolid. Linezolid is a water-soluble compound with a volume of distribution approximating total body water (40–50 L) and is readily distributed to most tissues (52–54). The half-life is approximately 4.5–5.5 hrs with the primary route of elimination being hepatic metabolism. Approximately 30% to 35% of the parent compound is excreted unchanged into the urine. Because of the water solubility and low protein binding (31%) of linezolid, significant clearance by dialysis would be anticipated (55–57).

The IHD-related pharmacokinetics of linezolid and the two major metabolites were evaluated in patients with end-stage renal disease and in patients admitted to the ICU (56, 57). The pharmacokinetics of 600 mg of linezolid IV were determined in five male critically ill patients with an Acute Physiology Assessment and Chronic Health Evaluation II score range of 23 to 29 with sepsis and renal failure (56). Approximately one third of the drug was removed; although there was substantial variability in the starting serum concentrations from patient to patient (56).

Linezolid clearance was evaluated in a single study performed in 15 critically ill patients with oliguric renal failure receiving SLED, CVVH, or IHD (Table 2) (57). Conventional IHD lasted 3–4 hrs with a blood flow rate of 300 mL/min and dialysate flow rate of 500 mL/min compared with SLED sessions of 8–9 hrs with blood flow rates of 200 mL/min and dialysate

flow rates of 100 mL/min. A low-flux polysulfone filter (F7HPS; surface area 1.6 m^2) was used for both IHD and SLED. CVVH was performed in two patients, both in the predilution mode with a reinfusion rate of 35 mL/min and blood flow of 150 mL/min at 10.5 hrs and 12 hrs each (58). Mean linezolid elimination was 193.7 mg (32.3% of the dose administered) with IHD, 205 mg (33.9%) with SLED, and 105 mg (17.5%) following CVVH. Because this was a single-dose study, the authors declined to make conclusive recommendations, although the data suggest linezolid clearance by 8- to 9-hr SLED sessions approximates that of IHD necessitating the re-administration of drug. With IHD, no dosage adjustment is recommended; however, IHD is usually only administered three times weekly. If SLED is utilized on a daily basis, an additional one third of the linezolid dose would be removed for each 12 hrs of dialysis and the serum concentration may drop below breakpoint values for enterococci, streptococci, and *Staphylococcus aureus*. We recommend that for a single SLED session of 8–12 hrs that no additional linezolid dose adjustment is necessary. However, if repeated sessions or prolonged (>12 hrs) periods of SLED are utilized, the clinician should consider an additional administration of 30% of the linezolid dose per each 12 hrs of SLED time.

Fluoroquinolones. The three most commonly used fluoroquinolones in the critically ill include ciprofloxacin, levofloxacin, and moxifloxacin (39, 59, 60). Although some similarities exist among the pharmacokinetic parameters of these agents, there are enough differences that dialysis clearance varies widely. In general, fluoroquinolones are lipophilic agents with low molecular weights and large volumes of distribution that are minimally affected in the critically ill (11, 28). They also all exhibit excellent oral bioavailability. However, whereas levofloxacin is primarily cleared renally, ciprofloxacin is cleared by both renal and hepatic mechanisms, and moxifloxacin is hepatically eliminated (61). In addition, ciprofloxacin and levofloxacin exhibit lower protein binding than moxifloxacin, although all range from 20% to 50% (11). Therefore, based on the pharmacokinetic properties of these agents, one would expect minimal dialysis clearance of moxifloxacin, with somewhat greater clearance of ciprofloxacin and substantial clearance of levofloxacin.

IHD dosing for these agents is reflective of their pharmacokinetics. Moxifloxacin requires no dose adjustment and may continue to be administered at 400 mg every 24 hrs. Ciprofloxacin should be dosed at 400 mg IV every 24 hrs in the critically ill to ensure attainment of target AUC/MIC ratios (11). Levofloxacin, with its greater extent of renal clearance and significantly prolonged half-life in renal disease (normal half-life 6–8 hrs, renal disease half-life >20 hrs), is dosed at 250–500 mg every 48 hrs, depending on disease state and severity (11). All doses should be given after dialysis sessions.

CRRTs require the use of adjusted doses for fluoroquinolones, except for moxifloxacin, which remains dosed at 400 mg every 24 hrs. However, due to the differences in clearance mechanisms between CRRTs dosing needs vary. CVVH doses tend to be lower than those required for CVVHDF, with CVVHD dosing in the middle, although due to the continuous nature of these modalities, the dosing approaches that of normal renal function patients (11). Ciprofloxacin dosing for CVVH is 200–400 mg IV every 12–24 hrs, with CVVHDF dosing at 400 mg every 12 hrs. Levofloxacin dosing may range from 250 mg every 24 hrs for CVVH to 250–750 mg every 24 hrs for CVVHDF (11). A loading dose of 500–750 mg may also be given for levofloxacin to assist in earlier attainment of pharmacodynamic targets (11).

Fluoroquinolone dosing in SLED remains under investigation. To date, one single-dose study of critically ill anuric patients receiving moxifloxacin or levofloxacin and SLED has been completed (Table 2) (61). SLED sessions were completed using a high-flux polysulfone filter (F60S; surface area 1.3 m^2) over 8 hrs with mean blood and dialysate flow rates of 161 ± 4 mL/min. In one study arm, ten patients received 400 mg of moxifloxacin infused over 60 mins, 8 hrs before SLED was initiated. Six of those ten patients had liver disease with a Child-Pugh score of class C. The clearance of moxifloxacin was estimated at 15.7 L/hr with a half-life of 12.3 hrs off SLED. Despite the lack of renal clearance for moxifloxacin, SLED itself added 2–3.1 L/hr of clearance, resulting in a half-life of 6 hrs during SLED. Even with the change in half-life, the pharmacokinetic parameters of moxifloxacin in the critically ill anuric patients appeared similar to those of healthy subjects and the presence of liver impairment did not seem to impact the drug clearance. Therefore, the authors recommended moxifloxacin at 400 mg every 24 hrs for patients receiving 8-hr SLED sessions.

In the second study arm, five patients received levofloxacin (250 or 500 mg) infused over 60 mins, 12 hrs before the SLED session was started (61). It should be noted that two of these five patients had received levofloxacin over 9 days before enrollment and were at steady-state. Drug clearance was calculated both on and off SLED. The estimated clearance of levofloxacin was 3.07 L/hr with a half-life of 34.5 hrs off SLED and a clearance of 2.93–3.12 L/hr with a half-life of 10.3 hrs for the 8-hr SLED session. The fraction of drug estimated to be removed by SLED was 17%–27%, which is similar to the percentage removed by IHD; however, the calculated half-life on SLED is similar to that in CVVH. The authors recommended adjusting the dose in SLED and administering the drug after SLED but did not provide specific dosing details (61). Based on the pharmacokinetic properties observed in this study and information available on CVVH dosing, we would recommend dosing levofloxacin at 250 mg every 24 hrs. If SLED is utilized as a continuous modality, the dose may need to be increased to account for additional clearance. Although ciprofloxacin shares some similar pharmacokinetic properties to other fluoroquinolones, there are insufficient data in SLED at this time to determine effects on those parameters. Based on the study discussed above and on CVVH data, dosing ciprofloxacin similar to CVVHD (400 mg IV every 12–24 hrs) could be considered at this time until more information is known.

Other Anti-Infectives

Echinocandins. All three echinocandins, anidulafungin, caspofungin, and micafungin, are highly protein bound (range 84%–99%) and have small volumes of distributions (volume of distribution at steady state 0.15– 0.6 L/kg) and relatively long half-lives (9–26 hrs) (61–65). Although limited data are available, no dosage adjustment during or after IHD is required with any of the echinocandins, principally due to their high protein binding (61– 65). No prospective trials have been published that evaluate the effect of CRRT dosing in patients receiving anidulafungin, caspofungin, or micafungin. Anidulafungin pharmacokinetics have been evaluated in a single

Table 3. Antimicrobial dosing recommendations during sustained low-efficiency dialysis

Drug	Nebraska Medical Center Dosing Recommendations[a,b]
Anidulafungin (66)	No dosing adjustments necessary
Daptomycin (25, 26)	Dose every 24 hrs on SLED Dose every 48 hrs off SLED
Gentamicin (32, 38)	Initial loading dose 6 mg/kg lean body weight every 48 hrs as a 30-min infusion. Give 1 hr before SLED. Doses should be adjusted according to serum concentrations observed during and after the SLED session[c] Non-ICU patients, dose every 24 hrs on SLED at approximately 2-2.5 mg/kg/dose (would recommend using ideal or adjusted body weight) Dose per levels off SLED Tobramycin–same recommendations Amikacin 15-20 mg/kg lean body weight every 48 hrs. Doses should be adjusted according to serum concentrations observed during and after the SLED session.
Ertapenem (51)	No dose adjustment needed
Meropenem, impenem (47)	Meropenem 500-1000 mg IV every 8 hrs while on SLED Imipenem 500 mg IV every 6 hrs while on SLED (if >70 kg)
Vancomycin (47, 48)	Dose every 12-18 hrs while on SLED Dose per levels off SLED
Linezolid (58)	No dose adjustment needed May consider supplemental dose or every 8 hrs dosing if continuous SLED for some organisms
Moxifloxacin, levofloxacin (61)	Moxifloxacin–no adjustment needed Levofloxacin–adjustment may be necessary, no specific recommendation

SLED, sustained low-efficiency dialysis; IV, intravenous; ICU, intensive care unit.

[a]These recommendations are used in our institution based on evaluation and interpretation of the literature and known properties of SLED. This information is not intended to replace clinical judgment or experience in individual patients; [b]dialysis parameters include blood and dialysate flow rates each set at 200 mL/min and the use of a high-flux polysulfone filter; [c]dialysis parameters include blood and dialysate flow rates each set at 300 mL/min.

patient undergoing SLED (Table 2) (66). A 63-yr-old male with *Candida albicans* cholecystitis associated with septic shock and acute renal failure was given 200 mg of IV anidulafungin over 30 mins followed by serial blood samples for analysis (66). SLED was performed over an 8-hr period with a dialysate flow of 180 mL/min and a blood flow rate of 180 mL/min with a high-flux polysulfone dialyzer (F60S; surface area 1.3 m^2). SLED had no impact on the plasma concentrations, which were comparable to healthy adults, and no measurable drug amount was found in the dialysate. The authors concluded SLED does not impact the pharmacokinetics of anidulafungin; therefore no dose adjustment is necessary, and clinicians should follow product label dosage recommendations for reduced renal function. We recommend following this statement with all echinocandins until additional information is available.

Ideal Study Design

Prospective pharmacokinetic studies in ICU patients can present a challenge due to the uncertainty of the disease course, the multiple procedures a patient may require that would interrupt dialysis, and difficulties obtaining consent for studies in critically ill patients. The majority of antibiotic studies in patients requiring SLED are single-dose pharmacokinetic trials that utilize various blood and dialysate flows (25, 26, 32, 38, 47, 48, 51, 58, 63, 66). Although these studies provide a foundation for dosing recommendations in clinical practice, there are limitations to the applicability of the data. Most patients in the ICU requiring SLED will be receiving more than one dose of an antibiotic agent and will receive repeated SLED sessions. Therefore, a study that examines the pharmacokinetics of multiple antibiotic doses both on-SLED and off-SLED would allow more accurate assessment of the impact of SLED on clearance. To facilitate this type of study, multiple blood and dialysate samples would be needed. If such a study were to be conducted, samples of blood and dialysate while the patient is on SLED, both before and after antibiotic administration, would provide adequate data to assess drug removal during SLED. It would be important to account for the patient's intrinsic clearance by including a urine output parameter in the study inclusion criteria. It would also be important to account for a minimum duration of SLED to ensure adequate time for drug removal. Operational characteristics of SLED (membrane type, surface area, method of CRRT, pre- and postfilter replacement fluid, sieving, and saturation coefficients) particularly blood and dialysate flow should also be standardized to best assess clearance, because those parameters will affect solute removal rates. Blood samples would also be required in the 24 hrs following the cessation of SLED to evaluate the re-equilibration of serum concentrations once the patient has returned to a drug-dosing regimen for reduced renal function (e.g., Cl_{cr} <10 mL/min). In addition, measured clearances of endogenous markers such as urea and/or β-2 microglobulin should be reported. This type of study would provide an improved approximation of the antibiotic dosing observed in clinical practice and may provide insight into drug accumulation effects and re-equilibration phenomena to allow for more precise dosing recommendations.

Institutional Practice Considerations

Although the study of antibiotic pharmacokinetics for patients receiving SLED is increasing, the available literature remains limited. Thus, there are numerous antibiotics for which no data are available necessitating dosing empirically or based on extrapolated data. At The Nebraska Medical Center, it is our practice to adjust those antibiotics for which renal dosing is normally necessary when the patient is on SLED, despite the lack of published pharmacokinetic data (Table 3). The standard blood flow and dialysate flow rates utilized for SLED at our institution are 200 mL/min and 100 mL/min, respectively. Dosage regimens are determined by using an estimated creatinine clearance of approximately 60 mL/min, which is based on data from SLED urea clearance studies (5, 6, 13). This may be a conservative estimate for antibiotic clearance, but we feel that it allows our critically ill patients to receive more aggressive dosing regimens and minimizes the risk of treatment failure from inadequate serum concentrations while also mitigating the risk of achieving supra-therapeutic serum concentrations. Therefore, we

utilize an on SLED-/off SLED-dosing regimen in which we dose the antibiotics with an estimated Cl_{cr} of 60 mL/min while on SLED and a Cl_{cr} of <10 mL/min in anuric patients while the patient is off SLED. However, off SLED dosing must be individualized if the patient is continued on IHD or to the patient's residual renal function if not receiving dialysis.

CONCLUSIONS

SLED poses a significant challenge with antibiotic dosing due to the extended duration and lower blood and dialysate flow rates. The potential for significant drug clearance and subsequent alterations in pharmacodynamics could potentially alter the treatment of bacterial and fungal infections. It is important for the clinician to have a clear understanding of how SLED differs from other forms of dialysis and its impact on drug clearance. Despite the potential for significant drug clearance, the dosing recommendations made within this article are based off very limited data, mostly single-dose pharmacokinetic studies in one patient, our extrapolation of the literature, and known pharmacokinetic and pharmacodynamic parameters. Often, our recommendations are based off our own experience; however, this should supplement sound clinical decision making. More clinical investigations are needed to support our extrapolations and recommendations for dosing antibiotic agents during SLED.

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