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Considerations for antibiotic dosing in critically ill patients requiring sustained-low efficiency dialysis

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OBJECTIVES

1. Compare and contrast sustained low-efficiency dialysis, intermittent hemodialysis, and continuous kidney replacement therapy.
2. Describe the pharmacodynamics and pharmacokinetic considerations to antimicrobial dosing in the critically ill patient requiring kidney replacement therapy.

BACKGROUND

Acute kidney injury (AKI) is a common complication of critical illness, affecting 35% of patients admitted to intensive care units (ICU) (Kumar & Singh, 2015; Pickkers et al., 2021). AKI is a sudden episode of kidney damage that happens within a few hours or days, leading to the buildup of blood waste products and difficulty maintaining fluid balance. Sepsis is a heterogeneous clinical presentation defined by physiological changes responding to an infectious etiology. Severe sepsis or septic shock leads to multiple organ dysfunction syndromes and is the primary contributor to almost 50% of AKI incidences in the ICU. AKI in the ICU is associated with a mortality rate of 45%. However, the mortality rate of sepsis-induced AKI has been reported to be as high as 70% (Bagshaw et al., 2007; Doi, 2016; Pickkers et al., 2021).

Approximately 20–30% of patients with severe AKI require kidney replacement therapy (KRT) (Harvey et al., 2021). KRT facilitates volume control, solute removal, correction of acid-base imbalances, and electrolyte disturbances. Sustained-low efficiency dialysis (SLED) is becoming a common dialytic modality in critically ill patients and is considered a conceptual and technical hybrid between intermittent hemodialysis (IHD) and continuous kidney replacement therapy (CKRT) (Brown & Battistella, 2020).

The intersection of AKI, SLED and sepsis afflicts a significant proportion of patients in the ICU with significant morbidity and mortality implications. As such, an understanding of the principles behind appropriate dosing of antibiotics in critically ill patients requiring SLED presents a valuable opportunity to optimize patient outcomes.

SOLUTE AND FLUID REMOVAL IN DIALYSIS

The dialysis circuit begins and ends with venous access and blood return to the patient. In most patients with AKI, the primary method of venous access is through a central venous catheter. Blood is pumped from venous access towards a filter called a dialyzer or artificial kidney outside the body. Blood enters at one end of the filter and is forced into multiple hollow fibers formed by the dialysis membrane. In hemodialysis, blood passes through the hollow fibers and a dialysis solution passes outside the fibers in an opposite direction to the blood-flow to facilitate solute and fluid removal. The blood exiting the filter is then pumped back into the patient's body.

Ultrafiltration describes the process of removing fluid from the patient. In dialysis, the force for ultrafiltration is generated by the pressure gradient of differing flow rates of blood and dialysate. Higher rates of flow are associated with a lower static pressure. As the flow rate of dialysate is usually higher than blood flow, fluid moves from the blood, through the membrane, and towards the dialysate. Convection refers to the transfer of solute across the membrane along with the bulk-flow of fluid during ultrafiltration. This phenomenon is also known as solvent drag. Large and small solutes are transported across the membrane with equal efficiency until the molecular radius of the solute exceeds the pore size of the dialysis membrane. Diffusion refers to solute transfer across the membrane down a concentration gradient and is the primary mechanism of removal of small/low molecular weight solutes (<1500Da) (Brown & Battistella, 2020).

The movement of drugs or other solutes through the dialysis membrane is largely determined by the size of the molecule relative to the size of the pores in the membrane. Modern high-flux membranes can remove drugs with molecular weights of above 20,000Da (Oshvandi et al., 2014). Generally, antibiotics are small molecules and fall below the threshold membrane permeability. As such, factors pertaining to the dialysis circuit that can influence the removal of antibiotics include the surface area of the membrane, the blood and dialysate flow and ultrafiltration rates, and the duration of dialysis therapy.

DIALYSIS MODALITIES

IHD provides rapid solute clearance and ultrafiltration during relatively brief treatments (3–5 hours), whereas continuous therapies provide more gradual fluid removal and solute clearance over prolonged treatment times (optimally 24 hours per day). Generally, SLED uses identical machines as hemodialysis, but is run for an extended period of time using lower blood and dialysate flow rates similar to CKRT. SLED is characterized by treatment times of 8–16 hours, but can be 24 hours in duration, with slower rates of solute clearance and ultrafiltration than IHD, but more rapid than CKRT. As such, dosing strategies used for patients on IHD or CKRT may not be translatable to those on SLED. The primary advantages of SLED are solute, fluid and acid-base control with improved hemodynamic stability compared to IHD, without the use of advanced and expensive machines, labour, and technical expertise required with CKRT (Bellomo et al., 1993; Berbece & Richardson, 2006; Patel et al., 2009). Table 1 compares and contrasts properties of the dialysis modalities that may be used in critical care.

Table 1

Comparing Dialysis Modalities

	CKRT	SLED	IHD
Advantages	Slow volume control with hemodynamic stability and good solute control	Slow volume and solute control, cost efficient with decreased workload	Greater volume removal in shorter period
Disadvantages	Costly and complex, frequent interruptions, continuous anticoagulation, high workload	Limited evidence with drug dosing	High ultrafiltration poorly tolerated, periodic solute and fluid control problematic
Treatment days per week	7 days	5–6 days	3–5 sessions
Hours/treatment	24 hours	8–24 hours	4 hours
Blood Flow (ml/min)	100–200	200–300	350–400
Dialysate Flow	20–30	300–350	500–800
Anticoagulation	Heparin or Citrate	Heparin or nothing	Heparin or nothing
Hemodynamic stability	+++	++	-

PHARMACODYNAMIC CONSIDERATIONS TO ANTIBIOTIC DOSING

Pharmacodynamics describe the pharmacologic response resulting from a drug once it reaches its site of action. The pharmacodynamics profile of antibiotics, whether it is concentration or time-dependent, often influences the drug dosing regimen. For antimicrobials that are concentration-dependent, a higher concentration relative to the minimum inhibitory concentration (MIC) of the organisms is the best predictor of the rate and extent of bacterial cell death. Antibiotics such as aminoglycosides and quinolones are considered concentration-dependent antibiotics (Table 2). For antimicrobials that are time-dependent, the best determinant of antimicrobial efficacy is the fraction of time the plasma drug concentration is above the MIC of the organism. The timing of antimicrobial administration relative to the initiation and duration of SLED is important to maximize either the time above MIC or peak concentration to MIC ratio in accordance with the pharmacodynamics properties of the drug and is an important consideration to balance the safety and efficacy of therapy (Levison & Levison, 2009).

DRUG PHARMACOKINETICS IN A SEPTIC PATIENT AND CONSIDERATIONS TO ANTIBIOTIC DOSING

Pharmacokinetics describe the movement of a drug through the body and are divided into four major components: absorption, distribution, metabolism, and elimination (Levison & Levison, 2009). Highlighted here are the general principles related to drug pharmacokinetics, the potential changes to these parameters during critical illness, and the considerations for antibiotic drug dosing in critically ill patients requiring SLED.

Table 2

Commonly Used Time Versus Concentration Dependent Antimicrobials

Time Dependent	Concentration Dependent
Penicillins	Fluoroquinolones
Cephalosporins	Aminoglycosides
Carbapenems	Metronidazole
Vancomycin	
Clindamycin	
Macrolides	
Sulfamethoxazole – trimethroprim	

Absorption

Absorption is the rate and extent a medication leaves the administration site and moves into the circulatory system, such as the transition of a drug given orally to systemic circulation. Bioavailability describes the fraction of an administered dose reaching systemic circulation. By definition, the bioavailability of an intravenously administered drug is 100%. For orally administered drugs, absorption depends on the amount of drug absorbed by the gut. Numerous drug and patient-specific variables can influence gut absorption. During critical illness and septic shock, the body's natural physiological response is to shunt blood to vital organs, including the brain and the heart. As such, the body reduces the blood flow and mobility of the gastrointestinal tract and compromises drug absorption from the gut. As enteral absorption is difficult to ascertain in the critically ill, intravenous routes of antibiotic administration are preferred to optimize systemic exposure (Smith et al., 2012).

Distribution

Volume of distribution (Vd) describes how well drugs distribute to the tissues. An important factor to consider in antibiotic therapy is the ability of the drug to penetrate to the site of infection. Generally, hydrophilic medications will remain in the plasma water volume and have a lower Vd, while lipophilic medications often have larger Vd. Often, deep seated infections such as those in the central nervous system or bone, require the use of antibiotics with large volumes of distribution. As drugs with large volumes of distribution have more drug distributed in tissue compared to the blood, these drugs will be dialyzed to a lesser extent (Smith et al., 2012). Examples of antibiotics with higher Vd include macrolides and fluoroquinolones.

A vital phenomenon affecting Vd and the extent a drug can be dialyzed is plasma protein binding. The predominant plasma proteins that drugs bind to are albumin and alpha-1-acid glycoprotein. These proteins are too large to cross the dialysis membrane, and drugs ⩾ 80% protein-bound are generally considered not significantly dialyzed. Similarly, highly protein-bound drugs cannot cross cellular membranes and distribute outside the vascular space. As such, high protein binding reduces the extent to which a drug can be dialyzed. High protein binding also reduces the apparent Vd. However, in critically ill patients, many conditions lead to plasma protein levels and binding changes. Accumulating organic acids (e.g. metabolic acidosis in sepsis) can compete with the binding of acidic antibiotics such as penicillins, cephalosporins, and aminoglycosides. In sepsis, increased vascular permeability and protein catabolism can decrease albumin concentrations. In critically ill patients with hypoalbuminemia, highly protein-bound drugs will have a greater fraction of free drug, leading to more significant pharmacological effects and potentially a greater extent of dialysis (Smith et al., 2012).

A patient's fluid status is vital in the antibiotic distribution in the critically ill. Fluid resuscitation is an essential intervention used in many septic patients, thereby increasing total body water. Complicating the increase in fluid status, many patients with septic shock will also have capillary leak syndrome creating an increase in interstitial volume and unpredictable intravascular volume, thereby causing unpredictable serum concentrations of antibiotics. However, the amount of antibiotics in the serum is often the active form responsible for the therapeutic effect. Changes to serum concentration after fluid resuscitation is more profound in hydrophilic antibiotics such as vancomycin, aminoglycosides and B-lactams. The failure to achieve effective serum drug concentrations can lead to therapeutic failure and increases the risk of antibiotic resistance. Strategies such as therapeutic drug monitoring for antibiotics like vancomycin and aminoglycosides, loading doses, reducing the interval between doses or using a continuous infusion for time-dependent antibiotics can support adequate serum concentrations when the Vd is increased (Smith et al., 2012).

Metabolism

The predominant site for drug metabolism is the liver. Drugs that are cleared by the liver are generally not affected by dialysis. However, some data from human studies show that liver drug metabolism may be affected by AKI. During critical illness, alterations in liver enzyme activity, serum protein concentration, and liver blood flow can result in clinically relevant changes in liver drug clearance. Unfortunately, how AKI affects hepatic drug metabolism is limited, and dose adjustments are difficult to predict (Brown & Battistella, 2020).

Elimination

Elimination describes the removal of drugs or their metabolites from the body. The kidney is the primary site of elimination for many antibiotics. However, in an AKI, repeated dosing can result in the accumulation of drugs or active metabolites, which may increase the risk for adverse drug events. Dialysis can replace the role of the kidney in removing drugs from the body. Generally, drugs that are readily eliminated by the kidneys are readily dialyzed. As such, administration of antibiotics is generally timed after or towards the end of dialysis sessions. However, for patients receiving 24-hour SLED, recent evidence suggests that it may be appropriate to dose certain antibiotics comparably to patients with uncompromised kidney function (Brown & Battistella, 2020).

Another important consideration for patients receiving kidney replacement therapy is whether they produce urine, as urine production indicates residual kidney function. If patients are not producing or produce little urine, antibiotic doses should be held on days these patients do not receive dialysis. In contrast, urine production suggests that the patient can eliminate some drugs and is not solely dependent on dialysis for drug elimination (Brown & Battistella, 2020).

CONCLUSIONS

Antibiotic dosing in the critically ill requiring SLED is complex and dynamic. An interprofessional approach should be undertaken with diligent patient assessment and care from the nursing team and medical team with consult from a clinical pharmacist. As there is little in the literature on antibiotic dosing in SLED, an individualized approach for each patient should be undertaken considering the dialysis regimen, patient presentation, and properties of the antibiotic therapy.

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