Renal Replacement Therapy in the Critically Ill Surgical Patient

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Kevin K. Chung and Ian J. Stewart

Introduction

The diagnosis of clinically significant acute kidney injury (AKI) among the critically ill surgical population occurs in approximately one in four admissions [1]. About 5 % of all patients admitted to the intensive care unit (ICU), or 1 out of every 20 admissions, require some form of renal replacement therapy (RRT) [1]. Among all critically ill patients who require RRT, the mortality has consistently been around 60 % [2]. Practically speaking, RRT refers to the clearance of excessive electrolytes, toxic solutes, and volume that accumulates in the intravascular and extravascular space in the setting of AKI. Most often, this type of therapy is delivered via a venovenous extracorporeal circuit with a blood pump that drives venous blood through an artificial "kidney" membrane. Less commonly, the peritoneal cavity could be used to exchange electrolytes and solutes in the form of peritoneal dialysis. We will focus our discussion in this chapter mainly on extracorporeal RRT with only a brief section on peritoneal dialysis.

Overview of Modalities

There are a number of RRT "modes" that can be used in the ICU. The various modes are typically divided into continuous RRT (CRRT) or intermittent hemodialysis (IHD) based on how long the therapy is applied and what type of machine is used. Regardless of the length of therapy, it is important to differentiate the two different ways that solutes can be cleared through a hemofilter within the context of an extracorporeal circuit. The two modes of clearance are "diffusive clearance" (a.k.a. hemodialysis) and "convective clearance" (a.k.a. hemofiltration). Before being able to understand this difference, we must understand the anatomy of a hemofilter, which does not differ significantly regardless of "mode."

Hemofilter Anatomy

Standard hemofilters that are utilized for the purposes of RRT are comprised of thousands of parallel hollow fibers encased in a cylindrical casing through which blood can flow (Fig. 15.1). These hollow fibers are analogous to tiny garden hoses with semipermeable walls, allowing small solutes and fluid to leak through the walls while blood is contained and passes through the middle portion of the fibers. In between the individual fibers naturally exists the "interstitial space" where leaked solutes can then escape through an opening in the cylindrical casing through the generation of a steady negative pressure or hydrostatic pressure alone.

Hemodialysis (Diffusive Clearance)

As blood flows through the fibers of a standard hemofilter, a port exists on one end of the outer cylindrical casing through which an electrolyte balanced solution (dialysate) can be infused to bathe the "interstitial space" and exit through another port on the other end of the outer casing. The steady flow of dialysate through this space creates a gradient between the concentration of any given electrolyte or solute in the blood contained in the hollow fibers and the concentration of the electrolyte or solute contained in the dialysate in the interstitial space. This concentration gradient allows solutes to passively move across the semipermeable membrane, from the space of high concentration, in the blood, to the space of low concentration, in the dialysate (Fig. 15.2). To

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K.K. Chung, MD (✉)
Burn Center, US Army Institute of Surgical Research,
Fort Sam Houston, TX 78258, USA
e-mail: kevin.k.chung.mil@mail.mil

I.J. Stewart, MD
Department of Medicine, David Grant Medical Center,
Travis AFB, CA 94535, USA
e-mail: ian.stewart@us.af.mil

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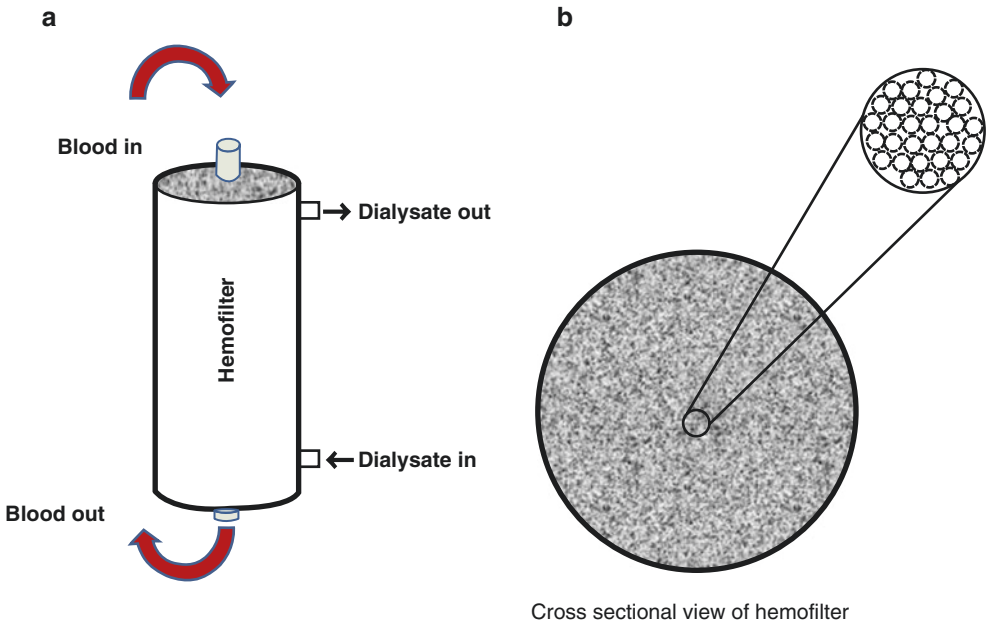

Fig. 15.1 (**a**) Schematic of a hemofilter used in this case for hemodialysis. The patient's blood enters the device at the top and is distributed into a multitude of semipermeable hollow fibers, demonstrated by the cross-sectional view (**b**). The patient's blood exists the filter at the bottom and is returned. Dialysate flows in a countercurrent fashion (i.e., the opposite direction of blood flow) to optimize the concentration gradient across the entire length of the hemofilter

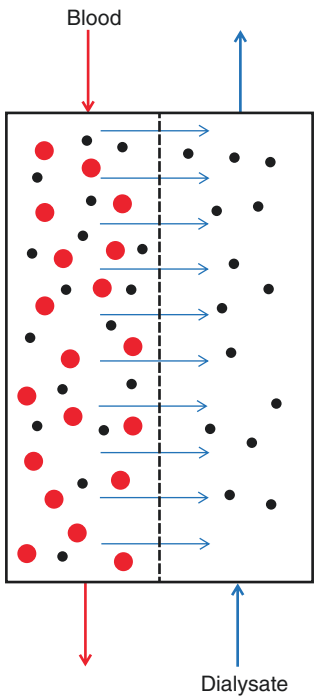

Fig. 15.2 Schematic representation of diffuse clearance in the setting of hemodialysis. Large particles (such as cells or albumin) are represented by the *red circles*. As these particles are too large to fit through the pores of the semipermeable membrane, they pass through the hemofilter and are returned to the patients. Small molecules (such as potassium and urea) are represented by the *black circles*. These molecules flow down their concentration gradient across the semipermeable membrane from the blood space to the interstitial space. To optimize the concentration gradient across the length of the hemofilter, the blood and dialysate go in opposite directions (countercurrent)

optimize the gradient between the two compartments, the dialysate is run in a countercurrent fashion (i.e., the blood and dialysate flow in opposite directions). This movement of solutes across a membrane down the concentration gradient is described as "diffusive clearance." Simply, dialysis removes various excess solutes from the bloodstream by maintaining a gradient to optimize "diffusion." Although highly efficient, this mode of clearance targets mostly solutes and molecules that are of low molecular weight in size (i.e., ≤10 kDal). Potassium and urea are examples of molecules that are in this range. Depending on the type of machine utilized, dialysate can be generated through the machine (IHD machines), come in premixed bags, or mixed by the hospital pharmacy.

Hemofiltration (Convective Clearance)

Hemofiltration, on the other hand, is a mode of solute removal that utilizes "convective clearance." In this mode, a negative pressure is generated in the interstitial space of the hemofilter, actively pulling solutes across the semipermeable membrane while an electrolyte balanced solution is introduced simultaneously either into the extracorporeal circuit or into the venous system of the body at the same rate (Fig. 15.3). This fluid is appropriately designated as "replacement fluid." Replacement fluid solutions are typically premade and commercially available in sterile packaging from various CRRT vendors. Alternatively, balanced crystalloid solutions, such as PlasmaLyte A® (Baxter Healthcare Corporation, Deerfield, IL), can be utilized as replacement solution. Of note, dialysate that is generated by IHD machines, typically through a reverse osmosis system

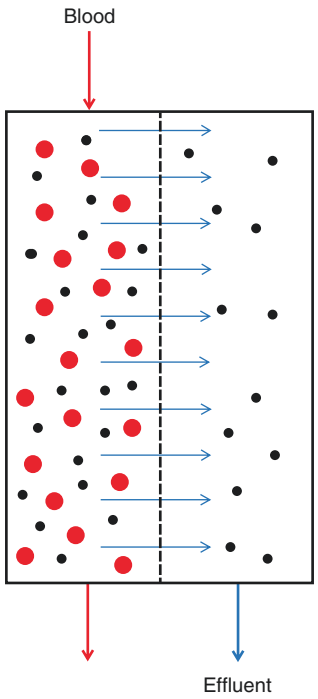

Fig. 15.3 Schematic representation of convective clearance in the setting of hemofiltration. With hemofiltration, there is no dialysate in the interstitial space. Negative pressure in the interstitial space pulls both solvent and fluid across the semipermeable membrane. Replacement fluid is infused either proximal to the hemofilter (pre-dilution) or distal to the hemofilter (post-dilution)

utilizing tap water, cannot be utilized as replacement solution as it is not considered "sterile."

Convective clearance, due to its active nature, can target solutes and molecules of higher molecular weight generally described as "middle molecules" (i.e., – 10–50 kDal). Examples of such molecules include beta2-microglobulin, most drugs such as antimicrobials, and pro- and anti-inflammatory mediators such as interleukin-1, interleukin-6, and interleukin-8. The ability of hemofiltration (convection) to remove such molecules has direct implications in the way electrolytes are managed, how drugs are dosed, and may impart extrarenal benefits.

Intermittent Hemodialysis

IHD describes a mode of extracorporeal therapy that is based on diffusive clearance and applied for a fixed period of time. Generally, IHD utilizes the same machines, personnel (dialysis technicians), and principles as chronic outpatient hemodialysis. In IHD, clearance is dependent on the blood flow rate and the dialysate rate. Treatments in the ICU, lasting 2–4 h in length, are prescribed three to five times weekly.

Compared to CRRT, IHD results in much greater clearances because of higher dialysate flow rates. This may be advantageous in patients that require high clearance (such as severe crush injury with rhabdomyolysis and resultant hyperkalemia). However, IHD may not be the preferred modality in critically ill surgical patients, because it can result in more hemodynamic instability than CRRT via two mechanisms. The first mechanism is due to the high clearance of IHD with resultant decrease in plasma osmolality [3]. When solute is removed from the intravascular space, equilibration from the extravascular space is not immediate. This establishes a gradient between these two compartments. Via oncotic pressure, water will flow out of the intravascular space leading to decreased blood volume. The second mechanism is due to the short treatment time during which volume can be removed. Similar to solute, equilibration of volume from the extravascular to the intravascular space is not immediate, and ultrafiltration can result in decreased blood volume. The rate at which volume is removed is therefore a key determinant in how a treatment is hemodynamically tolerated. For example, if 2 L of volume needs to be removed, the rate at which this occurs during a 4 h IHD treatment is 500 ml/h. This is much greater than the rate of ~83 ml/h that could be achieved using a continuous modality (2 L removed over 24 h). Therefore, IHD should only be used on hemodynamically stable patients, unless high clearances are required, for example, severe rhabdomyolysis with hyperkalemia that cannot be maintained at a safe level with a continuous modality. Decreasing the rate at which fluid is removed, by either increasing time or frequency, has been shown to decrease intradialytic hypotension in outpatient IHD [4] and can be considered in the critical care setting to minimize hemodynamic instability.

Continuous Modalities

Continuous modalities are typically delivered via machines that are specifically designed and marketed for inpatient use as CRRT machines. Unlike IHD, these machines typically do not utilize a water source (tap water) as they do not generate dialysate real time. Instead, the machines rely on premade sterile solutions that can be utilized for the purposes of both hemodialysis and hemofiltration. In fact, the exact same bag of solution can be labeled as "dialysate" or "replacement fluid" based entirely on how the solution is employed. The four modes described below are all commonly grouped under the term "CRRT." See Table 15.1 for suggested initial prescriptions.

Slow Continuous Ultrafiltration (SCUF)

In SCUF mode, a steady negative pressure is applied to the interstitial space pulling solutes and water across the semipermeable membrane and discarded through an opening in the outer filter casing through a tube that leads to an empty

Table 15.1 Typical starting prescription for the various modes of CRRT

Mode	Blood flow rate (BFR)	Replacement fluid rate	Dialysate flow rate	Ultrafiltrate rate (fluid removal)
SCUF	50–200 ml/min	None	None	50–500 ml/h
CVVH	100–400 ml/min	2–4 L/h	None	0–500 ml/h
CVVHD	100–400 ml/min	None	2–4 L/h	0–500 ml/h
CVVHDF	100–400 ml/min	1–2 L/h	1–2 L/h	0–500 ml/h

bag or directly into the sink. The fluid that is removed via this method is called "ultrafiltrate" and consists of only the fluid that is pulled across the semipermeable membrane while blood moves through the hollow fibers. This mode is typically prescribed to those who only need excess volume removed as in the case of patients with diuretic resistant fluid overload. Use of this mode is uncommon for surgical ICU patients as most have some degree of AKI and could benefit from the solute balance that is achieved through the other CRRT modes.

Continuous Venovenous Hemodialysis (CVVHD)

CVVHD is a mode of extracorporeal therapy that is based on diffusive clearance and applied continuously. CVVHD, being a mode of CRRT, is delivered by machines specifically designed for the ICU environment and utilizes premixed solutions. These solutions, typically in 5-L bags, are termed "dialysate" since it is used to provide the concentration gradient necessary for diffusive clearance.

Continuous Venovenous Hemofiltration (CVVH)

CVVH is a mode of extracorporeal therapy that is based on convective clearance and applied continuously. CVVH is also delivered by machines specifically designed for the ICU environment and utilizes premixed solutions. In contrast to CVVHD, these solutions, now termed "replacement fluid," are infused directly into the extracorporeal circuit and mixed directly with the circulating blood. Simultaneously, the negative pressure exerted in the interstitial space in between the hollow fibers of the hemofilter generates solute drag across the semipermeable membrane, removing solutes and water as the same rate that replacement fluid is being infused. The replacement fluid infusion can enter the circuit prefilter (proximal to the hemofilter), post-filter (distal to the hemofilter), or both depending on the type of machine used. The advantage of prefilter infusion of replacement fluid is a prolonged filter life that results from the dilution of blood prior to its entrance into the hemofilter. However, dilution of the blood also has the disadvantage of decreasing the efficiency of solute clearance. Post-filter infusion of replacement fluid optimizes efficiency but increases the chance of hemofilter clotting. Some CRRT machines allow the infusion of replacement fluid both pre- and post-filter. Regardless of where the replacement fluid is infused relative to the filter, an important concept to emphasize is filtration fraction. In an effort to minimize the hemoconcentration within the hollow fibers of the hemofilter, the filtration fraction must be kept below 25 %. Filtration fraction is simply calculated by adding all the effluent together and dividing it by the blood flow [5].

$$\text{Filtration Fraction} = \text{Total effluent} \left(\text{replacement fluid} + \text{ultrafiltrate}\right) / \text{blood flow}$$

The effluent consists of all the solute and water that is pulled into the interstitial space and directed out of the hemofilter casing into a waste bag or into a drain. This can be estimated by adding the replacement fluid rate and the additional ultrafiltrate set each hour. This equation is precise for post-filter infusion of replacement fluid. Prefilter infusion would further lower the filtration fraction by partially diluting the blood prior to it entering the hemofilter. Thus, this simple equation can be used as a rough estimate with the knowledge that the actual filtration fraction will always be lower if any portion of the replacement fluid is given prefilter.

Continuous Venovenous Hemodiafiltration (CVVHDF)

CVVHDF is a mode of extracorporeal therapy that utilizes both diffusive clearance (hemodialysis) and convective clearance (hemofiltration) applied continuously. Thus, a 5-L bag of premixed solution is connected to be infused as dialysate, while another bag is connected to be infused as replacement fluid. Although the same bag of solution, they are appropriately labeled differently based on the function the solution performs.

Hybrid Therapy: SLED

Slow low-efficiency dialysis (SLED) is a hybrid therapy of CRRT and IHD. In the literature, it is sometimes termed sustained low-efficiency dialysis, extended daily dialysis, or prolonged intermittent renal replacement therapy. The main advantages of SLED are that it can be performed with a conventional IHD machine, does not require specialized equipment, and requires less anticoagulation [6]. The differences between SLED and IHD are flows and time. In SLED, the

dialysate and blood flows are usually 100–200 ml/min, while in IHD the blood and dialysate flow rates are 350–400 ml/min and 700–800 ml/min, respectively. Conversely, while IHD is usually limited to 4 h, most SLED treatments last 8 h, but can be extended to 24 h which has been described as continuous SLED (C-SLED) [7]. Practically, C-SLED is no different than CVVHD; however the former usually involves higher dialysate flow rates. Otherwise, the only difference is that C-SLED is delivered using conventional outpatient machines, while CVVHD is delivered using CRRT machines that use premixed solutions. SLED allows for slower clearance of solute and volume, compared to IHD, which results in improved hemodynamic stability. The main disadvantage to SLED, particularly when treatments last more than 8 h, is uncertainty regarding appropriate dosing of essential medications (such as antibiotics) [8]. Additionally, staffing longer treatments for SLED becomes an issue if dialysis technician resources are limited.

There is a paucity of evidence comparing SLED to CRRT. A recent meta-analysis examined 17 studies (7 randomized controlled trials and 10 observational studies) that compared SLED to CRRT [9]. The investigators found a trend toward lower mortality in the observational studies but no difference in mortality in the randomized trials. This trend toward improved outcomes with SLED in the observational studies should be interpreted with caution given the inherent bias in these types of studies. The meta-analysis also reported no significant differences between CRRT and SLED in rates of renal recovery, fluid removal, length of ICU stay, clearance, or vasopressor escalation. However, SLED was less expensive in all three of the studies that reported on cost.

Overview of Controversies

Dose

Providers regularly prescribing or caring for critically ill patients on RRT must pay close attention to the dose of therapy. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommends frequent assessment of the prescription of and the delivery of actual dose [10]. At a minimum, RRT applied in the critically ill surgical patient should be able to achieve correction of any metabolic derangement or fluid imbalance for which the therapy was initiated. The nomenclature used for the dosing of RRT differs when describing IHD and CRRT. It should be noted that the highest grades (1A) were assigned for both dosing recommendations, reflecting strength and quality of the evidence that exists to result in those recommendations. For IHD, the KDIGO guidelines recommend delivering a Kt/V of at least 3.9 per week when prescribing either IHD or SLED in AKI [10]. Kt/V is a measure of the fractional clearance of urea, with K being the urea clearance (in L/h), t being time (in hours), and V being the volume of distribution of urea (in L, equal to total body water). As the units (L and hour) cancel out, Kt/V is a unit-less measure that describes the dose of IHD normalized for body size and time. Practically, this equates to a Kt/V of approximately 1.3 per IHD session for an every other day or three times a week schedule. A Kt/V of 1.3 equates to a urea reduction ratio (URR) of at least 60 % (depending on patient weight and ultrafiltration). Thus, if a patient is initiated on IHD with a blood urea nitrogen (BUN) level of approximately 100 mg/dL, the post-IHD level should be <40 mg/dL. For clinical use, however, modern dialysis machines have built-in conductivity sensors that can estimate Kt/V in real time. If this target dose is not achieved, the patient has been underdosed and could benefit from either more frequent IHD treatments or extended treatment times to achieve the minimum acceptable weekly dose recommended by KDIGO. For CRRT, KDIGO recommends delivering a total effluent volume of 20–25 ml/kg/h for AKI [10]. The total effluent volume consists of any fluid that flows through the interstitial space of the hemofilter to dump into the waste line into the effluent bag or into the sink. This can consist of ultrafiltrate only (SCUF), effluent with or without ultrafiltrate (CVVH), dialysate with or without ultrafiltrate (CVVHD), or dialysate plus effluent with or without ultrafiltrate (CVVHDF). All commercially available CRRT machines can display the total effluent volume (ml/kg/h) on the monitor.

Multiple studies have demonstrated that increasing doses beyond that recommended by KDIGO for both IHD and CRRT does not result in improved outcomes. The Veteran's Affairs and the National Institutes of Health Acute Renal Failure Trial Network study (ATN study) evaluated RRT dose in 1,124 patients [11]. The trial randomized patients needing RRT to either an intensive regimen of RRT or a less intense regimen. The intervention in the intensive group consisted of six sessions of IHD per week for hemodynamically stable patients and CVVHDF at a dose of 35 ml/kg/h or daily SLED for unstable patients. The less intensive group received three sessions of IHD per week for hemodynamically stable patients and CVVHDF at a dose of 20 ml/kg/h or every other day SLED for unstable patients. The Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group conducted their own multicenter trial, called the Randomized Evaluation of Normal versus Augmented Level RRT study (RENAL study) comparing high-dose CVVHDF (40 ml/kg/h) to lower-dose CVVHDF (25 ml/kg/h) in 1,508 patients [12]. Neither the ATN study nor the RENAL study demonstrated a survival advantage to delivering a higher dose of RRT regardless of mode.

Mode

The optimal mode of RRT in the treatment of surgical ICU patients has been the subject of much debate. As mentioned above, CRRT offers the advantage of being better tolerated

in hemodynamically unstable patients while allowing for slow and steady removal of volume over time when needed. However, a disadvantage is the need for continuous anticoagulation that increases the need for monitoring and, in turn, increases workload. IHD offers the advantage of rapid solute removal and rapid correction of electrolytes. There is also virtually no need for regional anticoagulation, and the intermittent nature of the therapy allows time for certain procedures and diagnostics without the need to interrupt therapy. Disadvantages of IHD include the potential for sudden fluid shifts which can be harmful in certain populations such as those with traumatic brain injury [13] with increased intracranial pressures and the potential for hemodynamic instability. The potential for hemodynamic instability can be mitigated by converting IHD to SLED and may be done seamlessly as long as staffing is available. CRRT is preferred in patients with brain injury because of the lower clearance offered by that mode. If CRRT is not available, SLED is an alternate mode for these patients. However, since SLED generally has larger clearances than CRRT potentially resulting in a greater osmotic shift, CRRT is the preferred modality if available.

Despite the theoretical advantages of one mode versus another, studies have demonstrated that at equivalent doses, no short-term survival advantage exists when comparing IHD to CRRT [14]. The KDIGO guidelines view IHD and CRRT as "complementary therapies" in the management of AKI in the ICU [10]. We are biased in favor of CRRT in most surgical ICU patients for the following reasons. First, KDIGO recommends choosing CRRT over IHD in hemodynamically unstable patients [10]. In many surgical ICU patient populations, such as burns [15], cardiothoracic [16, 17], or liver transplants [18], hemodynamic instability commonly accompanies acute care needs. Second, patients with intracranial hypertension from brain edema from any cause with AKI should be managed with CRRT over IHD [10, 13]. Lastly, long-term follow up studies, published after the KDIGO guidelines, suggest a possible advantage to a CRRT-based strategy in the ICU as less patients appear to be dialysis dependent when compared to an IHD-based strategy [19, 20]. It is quite compelling that among ATN trial survivors, the presence of dialysis dependence at discharge was 25 %, while among RENAL trial survivors, only 5 % of survivors were dialysis dependent [21, 22]. Thus, CRRT may be the therapy of choice in most surgical ICU patients.

Timing

The optimal time to initiate RRT in the critically ill surgical patient with AKI is also a controversial topic. Early studies showed benefit but were small in sample size [23]. Others suggest that early initiation in the critically ill is no better than waiting for clinical scenarios that would prompt the initiation of RRT in outpatients with chronic kidney disease who develop fluid overload or a metabolic disturbance of some kind (electrolyte imbalance, uremia, or acidosis) [24]. A recent systematic review suggested a possible beneficial impact on survival but concluded that the evidence was weak at best to make a strong recommendation [25]. Perhaps studies that are currently enrolling patients will help shed more clarity on this topic and help inform the nephrology and critical care community [26, 27]. Currently the KDIGO recommendation strongly encourages clinicians to consider the broader clinical context while identifying the specific conditions that can potentially be modified with RRT when considering initiation [10].

Clinical Considerations

Access

The KDIGO guidelines [10] suggest that RRT in the ICU setting be initiated with an un-cuffed, non-tunneled dialysis catheter. As has become the standard of practice, ultrasound guidance should be used for line insertion. The KDIGO guidelines recommend that access be preferentially placed in the right internal jugular vein. The second choice is a femoral vein and the third choice is the left internal jugular vein. This recommendation is based on balancing the need for adequate RRT and the infectious risk associated with central line placement. The right internal jugular vein is preferred because it is associated with the least amount of catheter dysfunction (defined as the ability to maintain adequate blood flows) [28]. However, this was only a trend ($p=0.09$) for femoral catheters compared to right internal jugular catheters. Clearance also appears to be equivalent between femoral and jugular catheters as long as a 25-cm catheter is used in the femoral vein. Conversely, the left internal jugular is associated with the most catheter dysfunction [28]. A concern with the use of femoral access is catheter-related bloodstream infection. However, in a randomized trial, femoral catheters were not associated with an increased risk of infection except in overweight patients (BMI >28.4) [29].

The use of subclavian catheters is discouraged in patients with AKI on RRT [10]. Because critically ill patients that require RRT are at an increased risk of developing end-stage renal disease [30], they may require permanent IHD access in the future. Central venous lines in the subclavian can cause central venous stenosis [31], which can complicate subsequent arteriovenous fistula placement. Therefore, the subclavian should only be used for access if no other options exist and, if needed, should be inserted on the dominant side [10].

Anticoagulation

While anticoagulation may be deferred in certain situations, such as patients with a coagulopathy or other contraindications, it is commonly used to prevent clotting of the filter. Filter clotting can decrease the amount of time on RRT, which impacts the delivered dose, and can also result in blood loss with subsequent transfusion requirement. If a patient requires systemic anticoagulation for another indication (such as a deep vein thrombosis or pulmonary embolism), it is adequate for the purposes of RRT. Otherwise, specific anticoagulation for the RRT circuit should be considered.

The most commonly used anticoagulants used to prevent clotting of RRT circuits are heparin and citrate. When heparin is used, a bolus of 2,000–5,000 units (or 30 international units/kg) can be considered, followed by a continuous infusion to maintain aPTT 1.5–2.0 times normal [32]. In patients with an elevation in aPTT at baseline (PTT > 35 s), the initial bolus can be deferred [33]. While a variety of citrate protocols have been described [34], the underlying concept is the same; citrate binds to calcium, decreasing the ionized calcium concentration. Because calcium is a key cofactor in the clotting cascade, this prevents filter clotting [35]. To avoid systemic hypocalcemia, calcium is infused in either the venous return line or centrally. When using citrate anticoagulation, the replacement fluid or dialysate should have a calcium concentration of 0 to avoid increasing the ionized calcium concentration within the circuit and reversing the anticoagulant effect. If a hypertonic solution compared to plasma is used, such as trisodium citrate (408 meq/L of sodium), the replacement fluid should be slightly hypotonic. Citrate also binds magnesium, therefore extra supplementation in the dialysate or replacement fluid should be considered. As citrate is metabolized predominantly by the liver to bicarbonate, the bicarbonate concentration should also be lowered to avoid alkalemia. If the citrate is not metabolized, such as in the setting of liver failure or profound hypoperfusion, citrate toxicity can occur. Citrate toxicity is characterized by an anion gap metabolic acidosis and a total to ionized calcium ratio of >2.5 (note that units must be equivalent). There are no citrate solutions that are approved by the Food and Drug Administration for anticoagulating an RRT circuit. In the United States, this requires the use of hypertonic citrate intended for blood banking purposes [36].

The optimal method for anticoagulation in RRT is not defined. On the basis of clinical trials demonstrating longer filter life and less bleeding complications, the KDIGO guidelines recommend citrate over heparin if the former is not contraindicated [10]. Since these guidelines were published in 2012, several other studies that compared heparin to citrate for anticoagulation have broadly confirmed these findings [37–39]. We agree that regional citrate should be considered first line for anticoagulation in CRRT. However, given the lack of standardized, approved citrate solutions and protocols, this should only be done at centers where physicians and nursing staff are comfortable with the technique.

Other anticoagulants such as argatroban can be used in the setting of heparin-induced thrombocytopenia, which requires systemic anticoagulation. One study used a loading dose of 100 μg/kg followed by a maintenance infusion of 1 μg/kg/min [40]. This maintenance dose was then titrated by 0.25 μg/kg/min to achieve a 1.5- to 3.0-fold elevation in aPTT. The authors found that measures of illness severity (APACHE II and SAPS II) could be used to predict the required maintenance dose. If argatroban is contraindicated, such as with severe liver failure, bivalirudin can also be used for anticoagulation in a CRRT circuit [41].

General Antimicrobial Dosing for RRT Recommendations (Table 15.2)

Optimal dosing varies based on agent, hemofilter, mode, dose, and patient characteristics which include protein binding, sieving coefficient, mode and dose of therapy, and volume of distribution. Please consult a critical care pharmacologist for more accurate initial dosing, maintenance, and monitoring.

Special Considerations

As already discussed, in the setting of traumatic brain injury, or other causes of increased intracranial pressure, CRRT is preferred over IHD. Greater clearance of IHD is not tolerated as well as CRRT from a hemodynamic standpoint. In the setting of increase intracranial pressure, this can result in decreased cerebral perfusion pressure and increased brain edema [13, 44, 45]. Another factor in patients with brain injury is anticoagulation. Systemic anticoagulation should be avoided in favor of no anticoagulation or regional citrate anticoagulation [44]. The final factor to consider in patients with brain injury is the serum sodium, which is usually kept artificially high to decrease edema. Commercially available solutions have fixed sodium concentrations, therefore additional hypertonic infusions of sodium should be given to maintain sodium at goal. For these reasons, CRRT is clearly the preferred modality in these patients.

Peritoneal dialysis (PD) is a form of RRT that utilizes the peritoneal membrane to achieve clearance via diffusion with fluid in the peritoneal space. The International Society for Peritoneal Dialysis (ISPD) has recently published guidelines for PD in the setting of AKI [46]. In the setting of AKI, it is

Table 15.2 General antimicrobial dosing for RRT recommendations

Antibiotic	IHD	SLED[c]	CRRT[e]
Vancomycin	15–25 mg/kg loading dose, then 500–1,000 mg after each IHD[a]	20 mg/kg loading dose[d]	15–20 mg/kg loading dose[d]
Daptomycin	4–6 mg/kg every 48–72 h, give after IHD on dialysis days	6 mg/kg every 24 h, give 2–12 h before treatment	8 mg/kg every 48 h
Piperacillin/tazobactam	2.25 g every 8–12 h, give after IHD on dialysis days	4.5 g every 8 h, infuse each dose over 4 h	3.375 g every 6 h, infuse each dose over 3 h
Cefepime	1,000 mg q 24 h, give after IHD on dialysis days	Not defined	Loading dose of 2,000 mg, then 1,000–2,000 mg every 12 h
Meropenem	500 mg every 24 h, give after IHD on dialysis days	500–1,000 mg every 8 h, time to infuse after end of treatment	1,000 mg every 8 h
Imipenem/cilastatin	250–500 mg every 12 h	Not defined	Loading dose of 1,000 mg, then 500 mg every 6–8 h
Levofloxacin	250–500 mg every 48 h	250–500 mg every 24 h	Loading dose of 500–750 mg, then 250 mg every 24 h
Amikacin	5–7.5 mg/kg every 48–72 h[b]	Not defined, dose based on drug level	Loading dose of 10 mg/kg, then 7.5 mg/kg every 24–48 h[f]

Modified from Scoville et al. [8] Additional references: Heintz et al. [42] and Jamal et al. [43]
[a]Redosing based on pre-IHD drug levels: <10 mg/L give 1,000 mg after IHD; 10–25 mg/L give 500–750 mg after IHD; >25 mg hold
[b]Redose when based on levels: Pre-IHD <10 mg/L; post-IHD <6–8 mg/L
[c]Assumes treatment for 8 h per day with blood and dialysate flow rates of 160 ml/min
[d]Give supplemental doses for goal trough of 15–20 mg/L
[e]Assumes effluent rate (sum of dialysate flow rate, replacement fluid and ultrafiltrate) of 25 ml/kg/h or 2 L per hour
[f]For severe infection, monitor level with goal peak concentration of 15–30 mg/L, redose when <10 mg/L

more commonly used in the developing world owing to its low cost compared to CRRT [46]. While there is limited evidence examining outcomes between PD and extracorporeal RRT methods, there is no evidence that one is superior to the other in terms of mortality [47]. When compared to CVVHDF, PD was not as effective in terms of creatinine and urea clearance or volume control [48]. However, the therapies were similar in terms of control of hyperkalemia and impact upon hemodynamics. Therefore, in an environment where IHD and CRRT are not available, PD should be considered for the primary management of severe AKI requiring RRT. In patients with impaired ability to convert lactate, such as liver failure or shock, bicarbonate-containing solutions are preferred over lactate-containing solutions as the former more rapidly corrects acidemia [49].

PD is also a method of home hemodialysis used for the chronic management of end-stage renal disease. Given changes to the way in which Medicare reimburses nephrologists, it is likely that this form of chronic RRT will become more prominent in the United States and thus may be encountered in the surgical ICU more frequently. We suggest that, if possible, PD be continued in such patients if they are admitted to the surgical ICU. However, if patients are catabolic, requiring more clearance, or volume overloaded, they may need to be transitioned to another form of RRT.

Novel anticoagulants used in the outpatient setting for atrial fibrillation, deep vein thrombosis, and pulmonary embolism may be encountered in the surgical ICU. One such is the direct thrombin inhibitor dabigatran. As there is no approved reversal agent for dabigatran, and the drug is cleared renally [50], these patients can present a therapeutic dilemma when they present with AKI. Dabigatran can be cleared by hemodialysis [50, 51] and hemodialysis has been shown to decrease the anticoagulant effect [51, 52]. As would be expected given the higher clearances inherent in IHD compared to CRRT, agent removal is higher with IHD [53]. Therefore, we suggest rapid initiation of IHD in patients with life-threatening bleeding in the setting of impaired renal function. Treatments longer than 4 h may be required to sufficiently clear the agent to have a clinically relevant effect [52, 53].

Discontinuation of Therapy

No specific guidelines exist for when to stop CRRT in the setting of AKI. The KDIGO Guidelines recommend stopping RRT when "it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs or because RRT is no longer consistent with the goals of care" [10]. In our practice, we

transition patients from CRRT to thrice weekly IHD when they are hemodynamically stable. An increase in urine output coupled with stability or improvement in serum creatinine between IHD sessions is our criteria for cessation of RRT in patients with AKI.

Emerging Concepts

While CRRT is the most widely utilized form of extracorporeal therapies available to clinicians, other emerging therapies exist that providers caring for critically ill surgical patients should be aware of [54]. All of these therapies come under the umbrella of extracorporeal life support (ECLS) and have been adopted at varying degrees. Extracorporeal membrane oxygenation (ECMO) has been utilized in the treatment of severe cardiopulmonary dysfunction for over 40 years. However, for years its use has been limited to just a few specialized centers around the world. Wider adoption of this ECLS technique has been spurred by one large randomized controlled trial demonstrating possible benefit [55] and the reports of its wide application during the 2009 H1N1 influenza outbreak [56]. Partial lung support, an extracorporeal therapy focused on CO2 removal, is an ECLS technique that most closely resembles CRRT in terms of the level of vascular access and blood flows [54]. In fact, some ECLS platforms have combined the ability to provide renal support and partial lung support to treat those patients who have concomitant pulmonary-renal dysfunction [57, 58]. Other ECLS applications include blood purification in septic shock and liver support in the form of molecular adsorbent recirculating system (MARS) or extracorporeal liver assist device (ELAD) [59]. Rapid advances in ECLS technologies have resulted in the emergence of the concept of multiple organ support therapy (MOST) which combines the various capabilities that are available in support of the critically ill surgical patient with multiple failing organ systems [59]. Clinician caring for the most critically ill surgical patients should become knowledgeable about these various emerging ELCS capabilities that go far beyond just renal support.

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