Management of Acute Kidney Injury/Renal Replacement Therapy in the Intensive Care Unit

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KEYWORDS

• Acute kidney injury • CRRT • Hemodialysis • Citrate anticoagulation

KEY POINTS

- Acute kidney injury (AKI) affects up to half of surgical ICU patients. The need for renal replacement therapy is associated with a mortality risk exceeding 50%. This article reviews the current best practices for the management of critically ill patients with AKI, with an emphasis on patients requiring dialysis.

INTRODUCTION

Acute kidney injury (AKI) is a syndrome characterized by an abrupt decline in kidney function. Multiple definitions have been used to define AKI in the past; however, a consensual classification for AKI definition was introduced in the year 2004[1] which defines AKI and its severity based on changes in serum creatinine concentration and degree of oliguria.[2] AKI is a common complication among patients in the intensive care unit (ICU). It is strongly associated with poor patient outcomes including high mortality rates,[3] prolonged hospital stay,[4] increased readmissions,[4] poorer health-related quality of life,[5] and higher likelihood for developing chronic kidney disease and end-stage renal disease.[6–8] This article presents current best practices for the management of critically ill patients with AKI, with an emphasis on patients requiring dialysis.

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY IN SURGICAL INTENSIVE CARE UNITS

AKI afflicts 50% of patients in ICU and is associated with poor short- and long-term outcomes. Nearly 5% of all ICU patients require renal replacement therapy (RRT) with a mortality risk exceeding 50% in these patients.[9] The incidence of AKI in surgical ICUs using the more recent consensus definitions for AKI varies by the reason for intensive care admission and the performed surgical procedure. AKI occurs in

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approximately 25% of ICU patients with blunt trauma and 40% of ICU patients with burn injuries.[10,11] Its incidence is approximately 5% following major abdominal surgeries such as gastric, pancreatic, and colorectal surgeries and 50% following major vascular surgeries or orthotopic liver transplantation.[12–14]

PATIENT EVALUATION OVERVIEW

Consensus definitions and staging systems for AKI were introduced and adopted to standardize diagnosis and reporting of AKI. The most recent definition and staging system are the Kidney Disease Improving Global Outcomes (KDIGO) staging system[15] which defines AKI and its severity based on changes in serum creatinine or urine output (**Table 1**). This staging system was adopted from prior definitions of AKI (AKIN[16] and RIFLE[2]). There are several limitations to the KDIGO staging system for AKI. It does not differentiate AKI based on the etiology of AKI. Different causes of AKI may differ in the specific intervention required and in the overall prognosis. To address this limitation, the KDIGO guidelines emphasize the need to promptly identifying the cause. Another limitation is the difficulty in establishing the baseline serum creatinine in patients who do not have a baseline measurement. In such cases, the first documented serum creatinine during hospitalization is often considered the baseline but this may result in delayed recognition of AKI if the onset of AKI preceded the hospitalization. Furthermore, serum creatinine can often be a delayed marker of AKI[17] and urine output may not be accurately recorded. Finally, several factors unrelated to kidney injury may affect serum creatinine, including the loss of muscle mass, large volume shifts, or drug effects.[18]

Blood or urinary biomarkers have the potential to improve the management and outcomes of AKI through stratifying patients for their risk of developing AKI, early detection of kidney injury, and phenotyping the kidney damage to enable a more tailored treatment. However, they have not yet fully made the transition to routine clinical care. Urinary biomarker [inhibitor of metalloproteinase-2 x insulin-like growth factor binding protein 7] is the first biomarker for the risk assessment of AKI to become available for clinical use in the United States. It has shown high sensitivity identifying critically ill patients at risk for developing stage 2 or 3 AKI within the subsequent 12 hours.[19] Two trials have shown a reduction in the incidence of AKI and its severity when preventative strategies (eg, early optimization of fluid status, maintenance of perfusion pressure, discontinuation of nephrotoxic agents) are implemented after cardiac and abdominal surgery in patients identified as high risk with the use of this biomarker.[20,21] The following causes of AKI should always be considered and explored in the surgical ICU setting.

ACUTE TUBULAR NECROSIS

ATN is the most common cause of severe AKI in the critical care setting, and most commonly results from renal ischemia (eg, hypotension or shock, cardiopulmonary

Table 1
Definition of AKI based on KDIGO guidelines

AKI Stage	Serum Creatinine	Urine Output
I	increase from baseline OR 1.5–1.9 x baseline	< 0.5 mL/kg/h x 6–12 h
II	2.0–2.9 x baseline	< 0.5 mL/kg/h x 12 h
III	3.0 x baseline OR Requiring renal replacement therapy	< 0.3 mL/kg/h x 24 h OR Anuria x 12 h

bypass), exogenous nephrotoxic insults (eg, iodinated contrast exposure, aminoglycosides, amphotericin B, vancomycin, or other medications), or endogenous nephrotoxic insults (eg, rhabdomyolysis, hemolysis). ATN is suggested by a history of renal insult and by the presence of granular casts or tubular epithelial cells on the urine sediment. Other supportive tests include urine specific gravity less than 1.015, urine osmolality less than 450 mOsm/kg (usually < 350), and fractional excretion of sodium (FENa) is greater than 1% in oliguric patients. FENa may be less than 1% in ATN in the presence of severe hypoperfusion or when ATN is secondary to contrast-induced nephropathy and pigment nephropathy (rhabdomyolysis, hemolysis). Treatment is primarily supportive. Hemodynamic abnormalities should be corrected, and potentially nephrotoxic agents discontinued. In some patients with severe AKI, dialysis may be required until renal function is restored. Some may remain dialysis dependent for up to 3 months or indefinitely.

ABDOMINAL COMPARTMENT SYNDROME

ACS is characterized by a sustained intraabdominal pressure of greater than 20 mm Hg in the presence of new organ dysfunction. Common culprits include intraabdominal or retroperitoneal hemorrhage, pancreatitis, massive fluid resuscitation, laparoscopy and pneumoperitoneum, and ileus. In critically ill patients, the incidence of ACS may be as high as 12%. Common early signs include tense abdomen, oliguria, elevated airway pressures, and difficulty ventilating. Management is supportive and includes surgical decompression when appropriate. Paracentesis may be needed in patients with tense ascites. Gastrointestinal decompression is required if ACS is due to intestinal distention. Sedation and chemical paralysis (in mechanically ventilated patients) may be required to relax abdominal muscles and to maintain adequate ventilation.

ACUTE URINARY RETENTION

Acute urinary retention may complicate surgical procedures and may lead to oliguria. It may induce vomiting, hyper- or hypotension, urinary tract infection, and arrhythmias. Anesthesia, perioperative medications such as opioids, surgical pain, and destruction of anatomy vital to voiding during pelvic surgeries may all play a role in the development of postoperative urinary retention. Risk factors include male sex, older age, diabetes, depression, and prostate hyperplasia. Diagnosis can be made by bladder scan showing more than 400 mL postvoid bladder volume. Management includes early ambulation when feasible and bladder decompression by intermittent or indwelling catheter.

ACUTE INTERSTITIAL NEPHRITIS

AIN generally occurs 10 to 14 days after exposure to a medication (earlier if patient was previously exposed). The most common medications that may cause AIN include beta-lactams, fluoroquinolones, sulfonamides, rifampin, H2 antagonists, proton pump inhibitors, allopurinol, and nonsteroidal anti-inflammatory drugs. Diagnosis is usually made by finding a temporal association between AKI onset and use of known culprit drug, or resolution with discontinuation of a drug. Biopsy may be considered when the diagnosis is not clear or when the withdrawal of a potential culprit drug may affect patient care. Signs and symptoms are nonspecific. The classic triad of fever, rash, and eosinophilia is observed in only 5% of cases. Urinalysis and urine sediment analysis may show proteinuria, glucosuria, white blood cells (WBCs), WBC casts, and red

blood cells. Nonsteroidal anti-inflammatory drug (NSAID)-induced AIN may present with nephrotic range proteinuria. Therapy with corticosteroid may be considered in those who have not responded to drug withdrawal. Steroids should be tapered and discontinued if no response is observed after 4 weeks of therapy.[22]

FLUID MANAGEMENT AND ACUTE KIDNEY INJURY

The goal of fluid therapy in the ICU is to optimize intravascular circulating volume and to maintain organ perfusion without causing fluid overload. Excessive fluid administration is associated with poor outcomes including the development of AKI.[23–28] Proposed mechanisms of volume overload causing renal injury include intrarenal compartment syndrome and venous congestion, and oxygen supply/demand mismatch. In patients with established AKI, fluid administration beyond correction of hypovolemia does not improve the possibility of renal recovery.[23] Oliguria should trigger an assessment of volume status but not be regarded as an absolute indication for fluid administration. The need for fluid therapy should be individualized based on the assessment of volume status in patients with signs of ongoing hypoperfusion and guided by hemodynamic indices that inform of fluid responsiveness (eg, respiratory variation of pulse pressure or stroke volume among patients mechanically ventilated or > 15% increase in cardiac output in response to a preload challenge). Patient's underlying diagnosis may also determine the fluid management strategy. For example, a conservative fluid administration strategy is often opted in acute respiratory distress syndrome (ARDS) as this approach has been shown to reduce the duration of mechanical ventilation without increasing the risk of kidney injury.[29] These findings were also applicable to the surgical cohort of patients included in the study.[30] In contrast, fluid restrictive strategy is avoided in the peri-operative settings. Indeed, restrictive fluid management when compared with liberal fluid strategy during and up to 24 hours after major abdominal surgery has been associated with higher risk of AKI and renal replacement requirement.[31]

The composition of crystalloid infusion may potentially impact kidney outcomes. Current evidence favors the use of balanced solutions for fluid resuscitation of patients at risk of AKI who are not hypochloremic, and the use of sodium bicarbonate in patients with moderate to severe AKI. The SALT-ED (Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department) and the SMART (Isotonic Solutions and Major Adverse Renal Events Trial) cluster randomized clinical trials compared saline to buffered crystalloids and the results support the preferential use of buffered crystalloids over saline.[32,33] Both trials showed a slight yet statistically significant a reduction in major adverse kidney events (a composite outcome of death, need for RRT and persistent kidney dysfunction) within 30 days in those who received buffered crystalloids than saline (SALT-ED, 4.7% vs 5.6%; SMART, 14.3% vs 15.4%). In patients with preexisting moderate to severe AKI and severe metabolic acidosis, the BICAR-ICU (sodium bicarbonate therapy for patients with severe metabolic acidemia in the ICU) clinical trial compared the effect of hypertonic sodium bicarbonate infusion with no infusion.[34] The trial suggested reduction in 28-day mortality and in the onset of one or more organ failures in patients. Interestingly, it also showed a reduction in the percentage of patients requiring RRT during ICU stay and on ICU discharge.

RENAL REPLACEMENT THERAPY

Timing of Dialysis Initiation in Acute Kidney Injury

Early initiation of dialysis based solely on meeting biochemical definitions of AKI has not been shown to provide mortality benefit in three multicenter randomized controlled

trials (RCTs).[25,26,35] The STARRT-AKI,[25] the largest and the most recent of the 3 trials enrolled 3019 patients and included a heterogeneous population including surgical patients. Critically ill adults with KDIGO stage 2 or 3 AKI were randomly assigned to either an accelerated RRT initiation (within 12 hours of randomization) or standard RRT initiation strategy based on clinical judgment and guided by a set of recommendations for initiation including (1) potassium level $\geq$ 6 mEq/L, (2) pH $\leq$ 7.20, (3) bicarbonate level $\leq$ 12 mEq/L, (4) Pao_2/fraction of inspired oxygen $\leq$ 200 mm Hg along with clinical perception of volume overload, or (5) persistence of kidney injury 72 hours after randomization. There was no difference in the primary outcome of 90-day mortality between the 2 groups (43.9% in accelerated vs 43.7% in standard; P = .92) and across subgroups stratified by sepsis, estimated glomerular filtration rate, type of admission (medical vs surgical), Simplified Acute Physiology Score II, and geographic region. Secondary outcomes that were similar between the 2 groups included the composite outcome of major adverse kidney events at 90 days, serious adverse events, ventilator-free days, and overall hospital length of stay. Interestingly, survivors of the accelerated group experienced greater RRT dependence at 90 days than the standard group (10.4% vs 6.0%; relative risk, 1.74 [95% confidence interval (CI), 1.24–2.43]) and there were more episodes of hypotension and severe hypophosphatemia in the accelerated arm.

In conclusion, the results of the 3 randomized trials do not support preemptive dialysis initiation based on the AKI stage alone. Decision regarding initiation of dialysis should be guided by the broader clinical contexts, the presence or absence of conditions that can be modified by dialysis, and the trends of laboratory abnormalities as advised by the KDIGO AKI guidelines.[15]

PRINCIPLES OF SOLUTE CLEARANCE AND ULTRAFILTRATION

RRT aims to control fluid management and solute clearance in the setting of kidney failure. **Fig. 1** illustrates the basic components of a dialysis circuit. The process of fluid removal is referred to as ultrafiltration. Solute clearance can be achieved by 2 primary means: hemodialysis – which relies on diffusion, or hemofiltration – which relies on convection. Diffusion is the flow of solutes down their concentration gradients across the dialyzer's semipermeable membrane. Diffusion is inversely proportional to its molecular weight in hemodialysis. On the other hand, convection is the process whereby solute is pulled across the dialyzer membrane during hemofiltration by solvent drag. Convection drags solutes regardless of their molecular weight provided the molecular diameter is smaller than the pores of the semipermeable membrane. Any volume removed by hemofiltration is replaced with physiologic fluids to avoid hypovolemia. This fluid is referred to as replacement fluid.

Medium molecular weight solutes such as beta-2 microglobulin, and inflammatory cytokines may be better cleared by hemofiltration as opposed to hemodialysis.[36] However, there is no clinical trial evidence to-date that supports the use of convective clearance (ie, continuous venovenous hemofiltration) over diffusive clearance (ie, continuous venovenous hemodialysis) in critically ill patients with AKI. A systematic review and meta-analysis comparing the 2 modalities in AKI showed no mortality difference, and no effect on RRT dependence or organ dysfunction.[36]

RENAL REPLACEMENT THERAPY MODALITIES

RRT for AKI in critically ill patients may be delivered in 3 different forms: intermittent hemodialysis (IHD), continuous RRT (CRRT), and prolonged intermittent RRT (PIRRT). The choice between the 3 modalities is dictated by the primary goal of therapy,

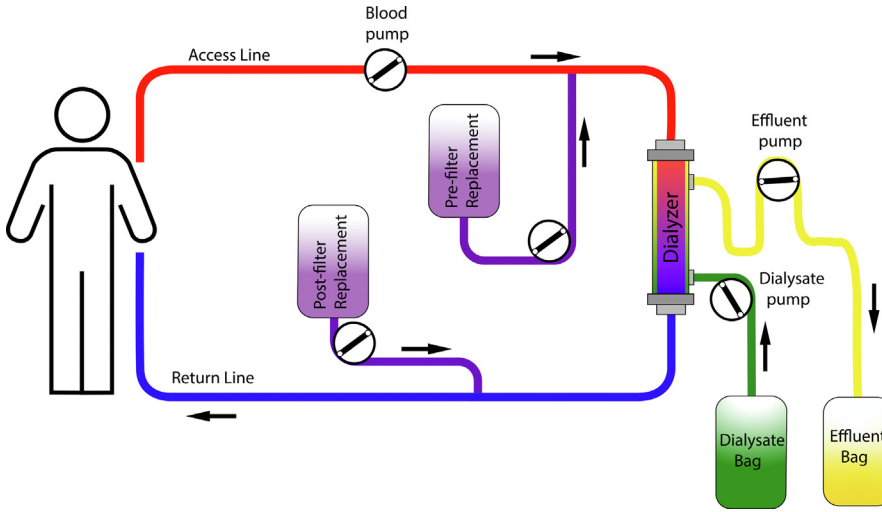

Fig. 1. Schematic illustrating the principal components of a dialysis circuit. Footnote. The patient's venous blood is pumped through the access line toward the dialyzer. In hemodialysis, dialysate flows countercurrent to the blood flow in the dialyzer, allowing for the maximum diffusive gradient between dialysate and solutes in the patient's blood. The dialysate fluid exiting the dialyzer is saturated with diffused solutes from the blood—this is called the effluent fluid. In hemofiltration, solutes are filtered across the dialyzer semipermeable membrane via solvent drag. The volume of fluid that is filtrated must be replaced with an equal amount of physiologic sterile fluid, either before or after the dialyzer.

metabolic disturbances, the degree of volume overload, and the patient's hemodynamics. **Table 2** summarizes the differences between these modalities.

IHD achieves rapid solute clearance and volume removal in a short period of time (typically 3 to 4 h). It is the modality of choice for the treatment of electrolyte derangements and drug poisonings that require rapid correction such as life-threatening hyperkalemia and acidosis, toxic drugs such as lithium, salicylate, and nonvolatile alcohol poisonings. Hemodynamic instability should not preclude the use of iHD with pressor support in metabolic emergencies such as severe hyperkalemia or life-threatening drug poisoning as these are situations that require prompt correction, and most efficiently managed with IHD.

CRRT is generally preferred in patients with hemodynamic instability, elevated intracranial pressures (eg, traumatic brain injury, cerebral edema, or acute liver failure), and severe dysnatremias.[15,37] Slow changes in plasma osmolality afforded by CRRT minimize fluid shifts between body fluid compartments and fluctuations in intracranial pressure. There are several modes of CRRT available, including continuous venovenous hemofiltration (CVVH) which relies on convection alone; continuous venovenous hemodialysis (CVVHD) which relies on diffusion alone; and continuous venovenous hemodiafiltration (CVVHDF) which combines both diffusive and convective modalities. The CRRT modality used at an institution is often dictated by CRRT machine capability and limitations, and protocols developed by the institution.

PIRRT is a hybrid between IHD and CRRT. It encompasses convective and/or diffusive methods of clearance delivery. Examples of PIRRT include sustained low-efficiency dialysis, extended daily dialysis with filtration, and accelerated venovenous hemofiltration or hemodiafiltration. It achieves slow clearance and ultrafiltration over 6 to 12-h periods. It can be helpful in situations whereby a patient may not tolerate hemodialysis but requires frequent interruption of CRRT for procedures.

Table 2
Characteristics of different modalities of renal replacement therapy

Characteristic	Intermittent Hemodialysis	CRRT	PIRRT
Typical blood flow rate (BFR)	400 mL/min	100–300 mL/min	100–300 mL/min
Typical dialysate flow rate	500–800 mL/min	16–40 mL/min	100–300 mL/min
Duration	3–4 h	Continuous	6–12 h
Advantages	• Rapid clearance of electrolytes and toxins: used for severe hyperkalemia and poisonings • Decreases ICU nurse staffing use • Allows time for rehabilitation • Often does not require anticoagulation	• Hemodynamic stability • Effective volume management • Continuous clearance helpful in high catabolic states • Minimizes effects on intracranial pressure	Compared with iHD: • Hemodynamic stability, easier volume management Compared to CRRT: • Decreases ICU nurse staffing use •Allows time for rehabilitation • Allows for more patient treatments per machine per day • May not require anticoagulation
Disadvantages	• Hemodynamic compromise • Volume management more challenging in some cases	• Filter clotting, requires anticoagulation • ICU nursing staff • Limits patient mobility • May not be able to use fistula access in ESRD patients	• Effects on intracranial pressure not well studied

There have been several studies comparing dialysis modalities in terms of mortality and RRT dependence. The studies are limited by selection bias, poor randomization, and high treatment crossover. A Cochrane review[38] and following meta-analysis of randomized controlled trials (RCTs)[39] demonstrated no difference in mortality or RRT dependence between CRRT and IHD. However, the meta-analysis did show that CRRT may be advantageous in minimizing hemodynamic instability and improving volume management. A systematic review of observational trials did show higher rates of dialysis dependence in survivors who were initially started on IHD as opposed to CRRT[40] but this has yet to be confirmed with RCTs. A single-center prospective RCT compared outcomes of PIRRT versus CVVH in ICU patients.[41] There was no mortality difference between PIRRT and CVVH. Patients who received PIRRT had fewer days of mechanical ventilation and fewer days in the ICU and required significantly less nursing care time related to RRT.

ACCESS TO RENAL REPLACEMENT THERAPY

An ideal dialysis access provides effective blood flow rates for RRT with minimal interruptions and recirculation between return and access lines.[42] It should also minimize complications such as thrombosis or infection. The 2012 KDIGO guidelines designate

the right internal jugular access as the preferred access choice, followed by femoral catheters and finally left internal jugular catheters.[15] Subclavian access is associated with increased risk of venous stenosis, jeopardizing chronic access options, and is therefore discouraged.[43] Femoral access has traditionally been linked to higher rates of infection, though some more recent studies have shown similar rates of bloodstream infections between jugular and femoral catheters,[44,45] except in patients with an elevated BMI.[46] Studies examining catheter dysfunction or filter life association with the type of access resulted in heterogeneous finding,[47] although there was a trend for left internal jugular access to be most associated with catheter dysfunction and shortened filter life. The length of inserted dialysis catheters should be considered carefully. To provide maximal unimpeded blood flow, a jugular catheter should terminate inside the right atrium as opposed to higher in the superior vena cava.[48]

Uncuffed nontunneled dialysis catheters (NTDC) typically serve as the preferred initial access modality in patients with AKI in the ICU, given the ease and timeliness of their insertion. However, tunneled dialysis catheters (TDC) may be associated with decreased rates of bloodstream infection,[49–51] likely due to the catheter cuff and tunneling under the skin. TDC are also associated with less dialysis interruptions and greater dialysis efficiency than NTDC,[52,53] likely due to the larger bore and catheter tip design, as well as their placement under fluoroscopy ensuring appropriate placement location. A prospective single-center cohort study comparing TDC to NTDC in both IHD and CRRT showed less dialysis interruptions, less mechanical complications, and higher median blood flow rates in the TDC group.[54] If it can be arranged in a timely manner, it is worth considering a TDC-first approach in patients with AKI who may require greater than 1 week of RRT, who have no active bloodstream infection and no significant coagulopathy.

In patients on extracorporeal membrane oxygenation (ECMO) and AKI, CRRT can be delivered either via a separate vascular access or by connecting the CRRT circuit to access points on the ECMO circuits. The CRRT circuit can be combined with the ECMO circuit in various ways. The advantages of each technique have been expertly described by many groups.[55]

DOSE OF RENAL REPLACEMENT THERAPY

Adequacy of dialysis in IHD is typically expressed by the function Kt/V, whereby K is the dialyzer clearance, t is the duration of dialysis, and V is the volume of distribution of urea). In contrast, dose of CRRT is expressed as effluent dose adjusted for body weight (in milliliters per kilogram per hour). Early small studies suggested better survival in patients with AKI with higher doses of dialysis.[56] It was hypothesized that a higher dose of RRT, particularly with convective modes, may help in clearing inflammatory mediators in the setting of sepsis, which may, in turn, translate into a survival benefit.[57]

Since then, 2 landmark studies established the optimal dose for RRT in patients with AKI.[58,59] The VA/NIH acute renal failure trail network (ARFTN) multi-center RCT[58] randomized 1124 patients between an intensive RRT arm (defined as CRRT dose 35 mL/kg/h or IHD 6 times weekly with a delivered Kt/V 1.2–1.4) or conventional therapy arm (CRRT dose 20 mL/kg/h or IHD 3 x weekly with a delivered Kt/V 1.2–1.4). Intensive RRT did not provide an additional benefit in 60-day mortality, duration of RRT or renal recovery. The RENAL trial[59] was another multi-center RCT that randomized 1508 patients between high-intensity RRT (CRRT dose of 40 mL/kg/h) and lower intensity RRT (CRRT dose 25 mL/kg/h). Again, there was no additional survival benefit or RRT dependence between the 2 groups. It is important to note that the delivered dose of

CRRT may not match the prescribed dose of CRRT. In the highly regulated context of these trials, the delivered dose of CRRT was anywhere between 84% and 102% of the prescribed dose. Retrospective studies have shown that, in practice, delivered CRRT can be as low as 68% of the prescribed dose.[60] This is likely due to treatment interruptions for procedures, filter clotting, among other causes.[61] Taking into consideration the time lost due to therapy interruptions, the current therapy guidelines recommend targeting a CRRT dose of 25 to 30 mL/kg/h. Although this guideline applies to most CRRT prescriptions, higher doses may be required in the setting of significant metabolic abnormalities such as hyperkalemia or severe metabolic acidosis which necessitate urgent reversal.

ANTICOAGULATION IN RENAL REPLACEMENT THERAPY

Blood is exposed to thrombogenic surfaces as it travels through the hemodialysis and CRRT circuits. Clotting within the dialyzer or hemofilter may compromise dialysis efficiency and in the event of circuit clotting, approximately 180 to 200 mL of blood may be lost. Therefore, some forms of anticoagulation techniques or periodic saline flushes are typically administered at the time of dialysis to prevent clotting in the blood circuit. For IHD, heparin anticoagulation may be used when not contraindicated. However, many hospitalized patients may be at increased risk for bleeding. Therefore, periodic saline flushes of the dialysis circuit without anticoagulation are considered by many as the preferred method of choice to maintain circuit patency in hospitalized patients. The high blood flow rates and the short duration of hemodialysis treatments (typically 3–4 hours) allow successful completion of the dialysis procedure with saline flushes in most patients.

Maintaining filter patency during CRRT is critical to optimizing delivered CRRT dose. The most commonly used agents for CRRT anticoagulation are regional citrate (RCA) and unfractionated heparin. The main disadvantage of heparin is that it causes systemic anticoagulation in addition to circuit anticoagulation and increases the risk of hemorrhagic complications.[62–64] RCA minimizes the risk of bleeding by restricting the effect of anticoagulation to the dialysis circuit. RCA uss a citrate infusion prefilter to chelate plasma ionized calcium within the dialysis circuit, thus eliminating a critical cofactor in the clotting cascade. The accumulated citrate is then largely cleared with dialysis. A small fraction is returned to the patient, to be metabolized by the liver into bicarbonate. The low plasma ionized calcium is maintained posthemofilter by zero calcium dialysate and/or replacement fluid. Low plasma ionized calcium in the return line is then corrected by calcium infusion either into the CRRT return line or into a central vein via a separate central line (**Fig. 2**).

RCA has been shown by numerous studies to be superior to heparin in terms of circuit life and bleeding complications.[65] However, RCA has not been universally adopted across all institutions administering CRRT.[9] Potential reasons for the slow adoption of RCA may include fear of metabolic complications (eg, hypocalcemia), the need for frequent RCA or calcium infusion adjustments, and the variability in published approaches.[66] Citrate can accumulate in patients with impaired citrate metabolism due to liver dysfunction.[67] In such patients, rising systemic citrate levels chelate calcium which causes low systemic ionized calcium. A total calcium to ionized calcium ratio (both in mmol/L) greater than 2.5 is recognized as an indicator of citrate toxicity.[68] Citrate toxicity is associated with increased mortality.[69] RCA protocols have been designed to completely abrogate the risk of citrate toxicity in patients with absent citrate metabolism, and to maintain systemic iCa levels above 1 mM using a personalized calcium dosing.[66,70] The 2012 Kidney Disease Improving Global

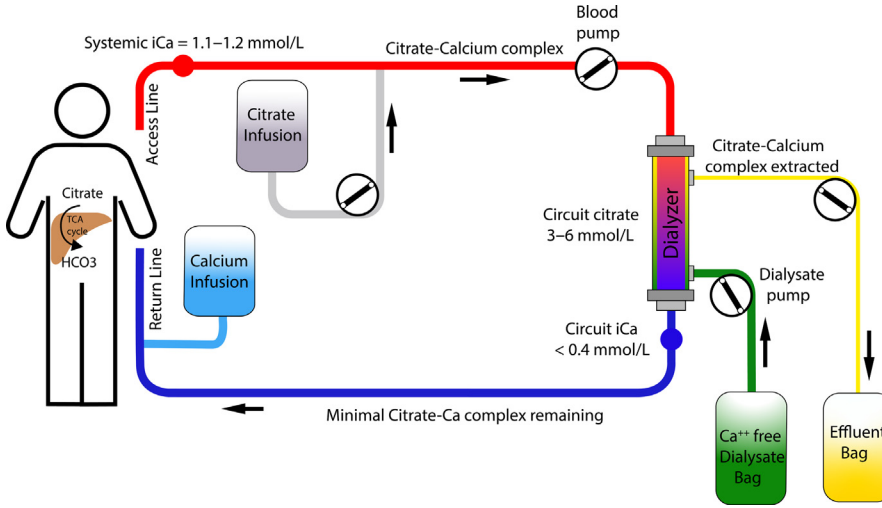

Fig. 2. Schematic illustrating the principals of regional citrate anticoagulation during continuous venovenous hemodialysis. Footnote. The patient's venous blood is pumped through the access line toward the dialyzer. Citrate is infused into the access line of the CRRT circuit. Citrate binds ionized calcium and lowers circuit ionized calcium to less than 0.4 mmol/L and achieves anticoagulation. The citrate-calcium complex is washed out in the dialysate. Anticoagulation in the return line of the CRRT circuit (ie, posthemofilter) is maintained using zero calcium dialysate. Calcium is infused into the CRRT return line to normalize ionized calcium levels just before the blood goes back into the patient.

Outcomes (KDIGO) AKI guideline advocates for citrate as first-line anticoagulation method for CRRT unless citrate is contraindicated.[15]

MEDICATION DOSING ON RENAL REPLACEMENT THERAPY

Retrospective reviews of drug dosing in hospitalized patients with renal dysfunction reveal dosing error rates ranging from 19% to 67%.[71] Such errors can be crucial in the ICU setting, particularly when it comes to antibiotic therapy, as sepsis remains the leading cause of death in the ICU.[72] Kidney failure and RRT introduce unique challenges to medication dosing in the critical care setting. Drug-related factors determining its removal during CRRT include the drug's molecular weight, its volume of distribution (V_d), and degree of protein binding. Drugs with larger molecular weights are removed less than drugs with smaller molecular weights at a given CRRT dose (when diffusive CRRT modalities such as CVVHD are used). The larger the V_d of a drug or the degree of protein binding, the less likely it is cleared by dialysis.

CRRT-related factors determining drug removal include the hemofilter features (eg, membrane, molecular weight cut-off, filter design), CRRT modality (eg, CVVH, CVVHD, or CVVHDF), or the CRRT dose (ie, effluent rate) for a dialyzable drug. A drug must be able to pass through the dialyzer membrane pores to be dialyzable. Drugs that are determined to be dialyzable should be dosed based on the effluent rate, with the guidance of therapeutic drug monitoring when available. Drug dosing should be evaluated on a regular basis in the ICU setting as patient conditions rapidly change. Changes in volume status, dialysis dosing, renal recovery, or transition to IHD should prompt review of the medication regimen and dose adjustment accordingly.

NUTRITION MANAGEMENT IN ACUTE KIDNEY INJURY

AKI generates an overall negative nitrogen balance as it leads to catabolism and muscle breakdown due to insulin resistance, metabolic acidosis, a proinflammatory condition, and the depletion of antioxidants.[73] This hypercatabolic state can be compounded by critical illness. AKI in the ICU puts patients at risk of malnutrition, which has been associated with complications related to wound healing, infections, and increased morbidity and mortality.[74] Nutritional support in patients with AKI should provide adequate macro- and micronutrients to avoid complications during the ICU stay. For patients who are not requiring RRT, standard energy and protein requirements for the general ICU patient applies: 25 to 30 kcal/kg/d with 1.2 to 2 g/kg of protein per day. Electrolyte restrictions depend on the degree of AKI and serum electrolyte profile.[75]

CRRT introduces challenges to nutritional support in the ICU. It is estimated that up to 10 to 15 g of amino acids are lost in 1 day of CRRT therapy. Patients on CRRT, therefore, require at least an additional 0.2 g/kg of protein a day, for a total of 2.5 g/kg/d, to achieve

Table 3
Micronutrients and trace mineral losses and recommended supplementation in CRRT

Micronutrient	Reported Losses in CRRT	Recommended Supplementation in CRRT per Ostermann 2021,[81] Honore 2013[82]
Water-Soluble Vitamins		
Vitamin B_1 (thiamin)	4 mg/d[83]	100–200 mg/d (low risk of toxicity)
Vitamin B_2 (riboflavin)	NR	2 mg/d
Vitamin B_3 (niacin)	NR	20 mg/d
Vitamin B_5	NR	10 mg/d
Vitamin B_6 (pyridoxine)	0.02 mg/d[84]	50–100 mg/d x 3–5 d and recheck levels
Vitamin B_7 (biotin)	NR	200 mg/d
Vitamin B_9 (folic acid)	290 μg/d[79]	1 mg/d
Vitamin B_{12} (cyanocobalamin)	NR	4 μg/d
Vitamin C	59–92 mg/d[79,85]	250 mg - 500 mg/d[a]
Lipid Soluble Vitamins		
Lipid soluble vitamins are typically not dialyzable[c,86]		
Minerals		
Zinc	Lost in RRT but possible positive balance may be due to the contamination of fluids[77,79,83]	5–10 mg/d
Selenium	Loss of 35–91 μg/d[83,85]	50–70 μg/d
Chromium	Loss of 18 μg/d[b,79]	10 μg/d
Copper	Loss of 200–400 μg/d[83,85]	1–2 mg/d

Abbreviation: NR, not reported.

[a] Avoid oversupplementation with vitamin C due to risk of oxalosis

[b] Despite losses with RRT, chromium is renally excreted, and some studies show higher levels in patients on CRRT.

[c] Reported cases of vitamin A toxicity and hypercalcemia in those receiving multivitamin with parenteral nutrition. Cautious with supplementation in the setting of kidney failure.

the appropriate nitrogen balance.[75] CRRT does provide additional caloric support through dextrose, lactate, or citrate that may be present in dialysate and replacement fluid therapies or acid-citrate-dextrose infusions. A prospective study of 10 ICU patients on CVVH estimated that an average of 512 kcal/d was delivered to the patients through the acid-citrate-dextrose formula A solution used in RCA.[76] The exact nutritional support delivered to the patient depends on the dialysate fluid composition and the CRRT prescription.

CRRT likely also leads to ongoing micronutrient vitamin losses. This is especially true for water-soluble vitamins which are more readily dialyzable, depending on their size. A retrospective study of patients on CRRT who had a micronutrient level measured during their hospital stay showed that several patients had evidence of below normal levels of thiamine and pyridoxine, as well as low levels of ascorbic acid, folate, zinc, and copper.[77] This was a retrospective study, so there was no opportunity to confirm that these micronutrients were lost in the effluent fluid. A prospective study by Ostermann and colleagues[78] investigated amino acid and micronutrient losses in patients in the ICU with severe AKI with or without CRRT. Patients on CRRT did have lower levels of citrulline, glutamic acid, and carnitine. Several amino acids were low among patients with AKI, both with or without CRRT. This was also noted in a prior small prospective study.[79] These findings do suggest that acute illness and AKI may lead to micronutrient deficiency independent of losses from CRRT. ESPEN guidelines[80] do recommend supplementation of water-soluble vitamins (particularly thiamine), selenium, and attention to serum calcium and magnesium levels in patients undergoing CRRT, though evidence for the clinical significance of this practice is lacking. **Table 3** provides reported losses of various micronutrients and their recommended daily supplementation during CRRT.

Enteral feeding electrolyte composition in the setting of CRRT depends on the serum electrolyte profile. Most patients can maintain appropriate serum potassium and phosphorus with no restrictions whereas on CRRT unless they have underlying cell or tissue breakdown. Patients will require phosphorus supplementation if the dialysate fluid does not contain any phosphorus. When transitioning from CRRT to hemodialysis, care must be taken to ensure that their diet is changed to a renal-restricted diet.

SUMMARY

AKI is a common complication among patients in the ICU. It is strongly associated with poor patient outcomes. Future study efforts should focus on measures to prevent AKI and develop tools for its early diagnosis. This would allow more prompt intervention to prevent worsening renal injury and improve outcomes. Observational studies and clinical trial data have provided some evidence-based guidance to best practices of care of patients with or at risk of AKI. However, many questions remain unanswered. We provide a summary of these studies as well as clinical practice recommendations that are guided by the conclusions of these studies.

CLINICS CARE POINTS

- Fluid therapy in the ICU should aim to optimize intravascular volume status and maintain organ perfusion, all while limiting volume overload which is associated with adverse outcomes.
- Current evidence favors the use of balanced solutions for fluid resuscitation of patients at risk of AKI who are not hypochloremic, and the use of sodium bicarbonate in patients with moderate to severe AKI.

- Priority should be made for a right internal jugular access site when placing a dialysis catheter. Subclavian access should always be avoided.
- Hemodialysis is the dialysis modality of choice for patients with severe hyperkalemia or acidosis, regardless of hemodynamic stability. Pressors can be used to support the patient while correcting metabolic abnormalities.
- CRRT is the dialysis modality of choice for those who are hemodynamically unstable or those at risk of cerebral edema or herniation.
- The current therapy guidelines recommend targeting a CRRT dose of 25 to 30 mL/kg/h
- Regional citrate anticoagulation is the preferred method of anticoagulation with CRRT.
- Dialyzable drugs should be dosed based on effluent rate, with the guidance of therapeutic drug monitoring. Changes in renal function or dialysis modality should prompt the review of medication dosing and schedule.
- Standard energy and protein requirements apply to patients with AKI who are not requiring RRT. We recommend against protein restriction in these patients.
- The daily nutritional requirements for patients on CRRT should account for their high energy demands, as well as amino acid and micronutrient lost in CRRT effluent. A protein requirement of 2.5 g/kg/d is anticipated. Supplementation with water-soluble vitamins is also necessary.
- When transitioning patients from CRRT to IHD, ensure that their diet is changed to a potassium, phosphorus restricted diet. Their medication regimen should be reviewed and appropriately dosed for hemodialysis.

DISCLOSURE

The authors have nothing to disclose.

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