Air Medical Journal 38 (2019) 311–314

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Critical Care Update

Renal Injuries, Markers, and Therapy

Anna Rauzi, BS, David J. Dries, MSE, MD

Recent critical care literature has seen an uptick of new information regarding iatrogenic renal insults. From the use of chloride-rich intravenous fluids to various forms of radiographic contrast, renal toxins creating insults associated with reduced renal function have been emphasized. At the same time, the literature is growing for markers of renal injury beyond the traditional trio of urine output, blood urea nitrogen, and creatinine. Although these markers have not reached full acceptance and the nephrology community has not identified optimal signs of early renal insults, biomarker identification has become an area of active research. Finally, most seriously ill patients are receiving renal replacement therapy (RRT) in a variety of forms. However, a surprising degree of controversy surrounds the timing of renal replacement therapies. The determination of timing for renal replacement appears to be moving back to initial classic indications.

Renal Toxins: New and Old

Kaplan LJ, Kellum JA. Fluids, pH, ions and electrolytes. *Curr Opin Crit Care*. 2010;16:323-331.

Van Regenmortel N, Verbrugghe W, Roelant E, et al. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. *Intensive Care Med*. 2018;44:409-417.

Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378:829-839.

Sen A, Keener CM, Sileanu FE, et al. Chloride content of fluids used for large-volume resuscitation is associated with reduced survival. *Crit Care Med*. 2017;45:e146-e153.

Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308:1566-1572.

Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. *N Engl J Med*. 2019;380:2146-2155.

The administration of both maintenance and resuscitation fluids in the setting of critical care has been implicated as a source of acute kidney injury (AKI). Intravenous fluids are often viewed as a routine element of inpatient care, but in the critically ill patient, fluid administration may be proinflammatory, excessive, and potentially injurious. Because of this, it is important to view intravenous fluids as drugs with therapeutic windows and adverse effects. Maintenance fluids are provided in low volumes and generally minimally affect electrolyte and acid-base balance. On the other hand, resuscitative fluids are often infused in large volumes at a rapid rate in order to reach physiologic end points in a critically ill patient. The composition of these fluids must be evaluated in order to properly treat patients who are at risk of AKI.

Saline and balanced crystalloids are 2 common types of routine fluids administered to critically ill adults. Although common, these agents have yet to be thoroughly investigated with regard to clinical outcomes. Historically, intravenous saline was the most common fluid administered to patients, but recent studies associate saline with AKI because of decreased renal perfusion through chloride-mediated renal vasoconstriction. Decreased renal blood flow promoting renal cortical hypoperfusion increases susceptibility to AKI.

An increasingly popular alternative to saline is the use of crystalloid solutions known as balanced crystalloids (eg, lactated Ringer solution or Plasma-lyte, Baxter International, Inc., Deerfield, IL). Balanced crystalloids contain an electrolyte composition closer to that of plasma and are now being investigated in relation to AKI. In a recent clinical trial conducted by Vanderbilt University Medical Center, researchers investigated the clinical outcomes of saline versus balanced crystalloid fluids in over 15,000 intensive care unit patients. The use of intravenous balanced crystalloids, rather than saline, resulted in a lower rate of persistent renal dysfunction, new RRT, and death by 1.1%. This significant difference in clinical outcomes between balanced crystalloid use and saline administration was noted to be greater in patients with sepsis and patients who received large volumes of isotonic crystalloid.

The mix of electrolytes in resuscitation fluids administered to critically ill adults is also important when determining the etiology of AKI. In fluid resuscitation, the use of crystalloids that contain higher chloride concentration has been associated with higher rates of hyperchloremic acidosis when compared with balanced crystalloid administration. Hyperchloremic acidosis has been implicated in hemodynamic instability, a decline in renal function, and decreased survival. In large volume resuscitation, the

1067-991X/$36.00

https://doi.org/10.1016/j.amj.2019.07.011

use of fluids containing supraphysiologic amounts of chloride has been associated with long-term mortality. One explanation for this finding is the possibility that supraphysiologic chloride solutions may complicate underlying problems that are present in critically ill patients such as acid-base imbalances or preexisting renal deterioration.

Until recently, the relationship between chloride concentration and the prevalence of AKI in critically ill patients has been solely investigated in the realm of resuscitation fluids. It is important to note that maintenance fluids can also be implicated in the deterioration of renal function. Antwerp University Hospital found that the overuse of maintenance fluids can be just as, if not more, deleterious than resuscitation fluids. On average, resuscitation fluids make up 6.5% of the daily total fluid administered, whereas maintenance fluids make up 24.7% of the daily total fluid volume, far exceeding that of resuscitation fluids. Researchers believe much toxicity of chloride can be attributed to fluid volume administered unintentionally over time. With this unintentional administration of chloride, the likelihood of acquiring AKI increases. The concentration of electrolytes within fluids administered can impact the outcomes of patients who require acute large volume resuscitation and maintenance fluids.

Because of the significant increase in mortality associated with a chloride-liberal fluid regimen, a chloride-restrictive fluid administration strategy may be more favorable. In a prospective clinical study at the University of Melbourne, researchers found that a chloride-restrictive fluid regimen was associated with a significant reduction in the occurrence of AKI. Another proposed explanation for the detrimental effects of chloride-liberal fluid administration may be activation of tubuloglomerular feedback, a physiological process that regulates the glomerular filtration rate. This feedback loop triggers afferent vasoconstriction and reduces the glomerular filtration rate.

In order to avoid a decrease in renal function and a subsequent increase in the likelihood of AKI, the composition, concentrations, and quantities of intravenous fluids administered to critically ill adults must be acknowledged in the prophylactic treatment of AKI.

Although multiple recent reports warn of toxicity associated with chloride administration in routine intravenous fluids, radiographic contrast–associated AKI has been reported since the 1950s. Historically, contrast-associated kidney injury is defined as a rise in plasma creatinine occurring within days after exposure to contrast agents. Pathological mechanisms by which contrast agents cause kidney injury remain unclear. Direct and indirect effects as well as hemodynamic perturbation have been suggested. Contrast agents are toxic to tubular epithelial cells, leading to loss of function with both apoptosis and necrosis. Indirect mechanisms of renal injury related to contrast administration have also been related to ischemic injury caused by vasomotor changes mediated by endothelin, nitric oxide, and prostaglandins. The outer renal medulla has a relatively low partial pressure of oxygen leading to enhanced risk for injury when coupled with increased metabolic demand of critical illness, making the medulla particularly susceptible to adverse hemodynamic effects of contrast material.

The risk of kidney injury after the administration of contrast material is also affected by patient- and procedure-related factors. Preexisting chronic kidney disease is the strongest patient-related factor leading to contrast-associated renal dysfunction. In patients undergoing percutaneous coronary interventions in large retrospective studies, severe chronic kidney disease was the strongest independent risk factor for contrast-associated kidney injury. Remarkably, diabetes is not seen as an independent risk factor but rather an amplifier of patient susceptibility in the presence of underlying kidney dysfunction. With multiple contrast agents now available, low osmolality or iso-osmolality agents are associated with a reduced risk of kidney injury as opposed to older, high osmolality agents. In addition, the use of large volumes of contrast material (300 mL or > 4 mL/kg) or repeated administration of contrast within 72 hours after the initial administration has been associated with an increased risk of renal injury. A particular high-risk group based on procedure is individuals with ST-segment elevation myocardial infarction who undergo percutaneous coronary interventions. It is also generally believed that arteriography is associated with a higher risk of contrast-associated kidney injury than computed tomography using contrast because of the delivery of a more concentrated contrast load to the kidneys with arteriography and the higher overall risk profile of patients requiring these procedures. Many studies have shown that contrast-associated AKI is associated with increased mortality.

Despite historical data tying contrast administration to kidney injury, severe kidney injury, characterized by substantial deterioration in function or the need for RRT, appears to be infrequent after intravascular contrast administration. Thus, the best approach to care of patients undergoing contrast-enhanced procedures involves the implementation of preventive strategies. The most common preventive strategy is intravascular volume expansion. Literature supporting volume expansion as a preventive strategy for AKI is remarkably inconsistent. In addition, despite the comments made about chloride earlier, small trials including volume expansion with alkalizing agents do not show consistent benefit. Although careful use of volume expansion will be continued, additional data regarding details of this therapy are needed. Of medications proposed as renal protective agents in the setting of contrast administration, current evidence gives the greatest support to statin administration. Unfortunately, trials of statins as prophylaxis against contrast-associated renal injury are limited because of small sample sizes and the fact that many patients have preexisting administration of statins for a variety of indications. Thus, isolating the impact of statins on contrast-associated renal injury remains problematic.

Markers of Renal Injury

Haines R, Crichton S, Wilson J, et al. Cardiac biomarkers are associated with maximum stage of acute kidney injury in critically ill patients: a prospective analysis. *Crit Care*. 2017;21:88.

Gocze I, Koch M, Renner P, et al. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. *PLoS One*. 2015;10:e0120863.

Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J*. 2013;6:8-14.

Pianta TJ, Peake PW, Pickering JW, et al. Evaluation of biomarkers of cell cycle arrest and inflammation in prediction of dialysis or recovery after kidney transplantation. *Transpl Int*. 2015;28:1392-1404.

Klein SJ, Brandtner AK, Lehner GF, et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med*. 2018;44:323-336.

Beyond urine output, blood urea nitrogen, and creatinine, a remarkable number of biomarkers suggestive of renal injury have been investigated. A recent review identified 62 biomarkers. Of these, 31 biomarkers were measured in blood, and 31 biomarkers were present in the urine. Urinary biomarkers are of particular interest because damage in AKI first appears in renal tubular cells. Thus, urinary biomarkers are thought most sensitive for the diagnosis of AKI.

Of the available urinary biomarkers, urinary neutrophil gelatinase–associated lipocalin (NGAL), urinary interleukin 18,

and urinary cystatin C have received the most attention. Other markers include urinary N-acetyl beta-D glucosamine. Although these and other markers have been associated with kidney injury, time-honored parameters such as fractional excretion of sodium are comparable in predictive value.

NGAL is found in the blood as well as the urine and has been studied widely. Cystatin C from blood samples has also been investigated. Some of these biomarkers have been combined in prediction studies with creatinine and other traditional renal performance data. For example, plasma NGAL combined with creatinine more effectively predicts AKI than either marker independently. Unfortunately, the overall predictive value remains poor. Of the biomarkers studied, the largest number of studies are available for NGAL. Of the biomarkers measured in the blood, cystatin C is the more effective predictor followed by creatinine. NGAL and cystatin C are likely the best biomarkers obtained in the urine at present. Another trend, combinations of biomarkers such as tissue inhibitor of metalloproteinase-2 and insulinlike growth factor binding protein 7, provides a more effective prediction of AKI compared with either biomarker alone. These biomarkers are both involved in early cell cycle arrest, reflecting initial stages of kidney injury. Among biomarkers in blood, cystatin C performs best followed by NGAL and plasma or serum creatinine. Cystatin C directly reflects glomerular filtration in chronic kidney disease as well as AKI. Because this marker is directly related to renal tissue function, it demonstrates AKI earlier than creatinine.

As we presently understand them, individual biomarker measurements may provide incremental support to guide clinical decision making. It is clear from available data that these tests should not be used in isolation. A promising approach seems to be a combination of biomarkers and common clinical parameters. Unfortunately, relatively few studies have taken this approach. Another important consideration relevant to the evaluation of biomarkers is the time point of assessment. Not all biomarkers have the same window of presentation. Urinary vascular endothelial growth factor has good predictive value immediately after a renal insult, but effectiveness declines over the following 12 hours. Biomarkers presenting earlier such as tissue inhibitor of metalloproteinase-2 and insulinlike growth factor binding protein 7 become more effective predictors over the first 12 hours after renal injury. Thus, the relevance of biomarkers is also clearly related to the time of collection relative to a renal insult.

Renal Replacement Therapy

Acute kidney injury and renal replacement therapy. In: Marini JJ, Dries DJ, eds. Critical Care Medicine: The Essential and More. Baltimore, MD: Wolters Kluwer; 2019:609-625.

Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315:2190-2199.

Gaudry S, Quenot JP, Hertig, et al. Timing of renal replacement therapy for severe acute kidney injury in critically ill patients. *Am J Respir Crit Care Med*. 2019;199:1066-1075.

Tandukar S, Palevsky PM. Continuous renal replacement therapy: who, when, why, and how. *Chest*. 2019;155:626-638.

Terminology surrounding RRT is confusing. Each technique is derived from 3 basic characteristics: the method used to remove solutes (diffusion, convection, or a combination), whether the process is intermittent or continuous, and the access site (arteriovenous or venovenous). The 2 basic methods of fluid and solute removal are hemofiltration in which fluid and solutes are removed from blood by convection (hydrostatic pressure gradient removing solute from blood across a semipermeable membrane) and hemodialysis in which solutes diffuse from blood across a semipermeable membrane down a concentration gradient created by the dialysate used. These techniques may be combined as hemodiafiltration in which diffusion and convection remove fluid and solute from the blood.

In its simplest form, hemofiltration removes solutes in exactly the concentrations in which they are present in blood as they are passively carried across a semipermeable membrane in the dialysis circuit. Decreases in solutes such as plasma urea or creatinine concentrations result from the replacement of extracted ultrafiltrate with nonurea or creatinine-containing electrolyte solutions, which in essence dilute the plasma. Hemofiltration is typically performed continuously. Continuous therapies have several advantages over intermittent therapy. One advantage is the ability to be conducted safely by a critical care nurse in the intensive care unit. Another benefit of continuous therapy is that it is much less likely to result in hemodynamic instability or cerebral edema than intermittent therapy, in part because of slower changes in plasma solute concentration. Continuous RRT has become a favorite technique to treat the hemodynamically unstable patient.

Hemodialysis differs from hemofiltration because the dialytic fluid on the other side of the semipermeable membrane creates a concentration gradient, facilitating removal of solute from the blood. Because the membrane in a hemodialysis unit is permeable in both directions, electrolytes in dialysate equilibrate with those of plasma. Thus, electrolyte composition of dialysis fluid should roughly approximate desired plasma electrolyte concentrations. Although it is more efficient than hemofiltration, hemodialysis requires cardiovascular stability; rapid shifts of fluid between intracellular and extracellular compartments may be induced by changes in plasma solute concentrations that are not well tolerated by hemodynamically unstable patients. Hypotension during hemodialysis is the most common significant problem.

Without a specific indication, the optimal timing for the initiation of RRT in AKI is unclear. Early initiation of RRT allows for the optimization of volume status, early correction of electrolyte and acid-base disturbance, and control of azotemia before the development of metabolic disturbances that form the list of emergent indications for RRT. However, the potential benefits of the early initiation of RRT need to be balanced with the risks and burdens associated with RRT including vascular access (hemorrhage, thrombosis, vascular injury, and catheter-related infection), intradialytic hypotension that could cause secondary renal injury, and resource use along with potential concern that RRT may impair subsequent recovery of kidney function. In addition, it is often uncertain whether an individual patient will have persistent AKI or rapid recovery of renal function because currently there are no tools to reliably predict the clinical trajectory for the individual patient with AKI.

Multiple observational studies suggest improved survival associated with earlier initiation of RRT. These studies are limited in that they include only patients who ultimately received RRT and did not account for patients with AKI who did not undergo early RRT and either recovered kidney function or died without receiving RRT. Excluding these patients from analysis results in potential bias because the actual clinical question is not one of early versus late initiation of RRT but rather early versus later RRT in patients in whom there is no urgent indication.

A number of recent trials have been performed to study the timing of RRT. Unfortunately, there is discordance in the results of these trials. The Effect of Early versus Delayed Initiation of RRT on Mortality in Critically Ill Patients with Acute Kidney Injury (ELAIN)

trial was a single-center, unblinded randomized controlled trial of 231 critically ill patients at a single university hospital in Germany. Patients enrolled in the early RRT administration group had stage 2 AKI (doubling of serum creatinine level or urine output < 0.5 mL/kg/h for 12 hours). Patients were randomized to receive either immediate initiation of RRT or a strategy in which RRT was delayed until an absolute indication for this therapy was identified or AKI had progressed to stage 3 (tripling of serum creatinine, urine output < 0.3 mL/kg/h for 24 hours, or anuria for 12 hours). All 112 patients in the early arm and 108 of the 119 patients in the delayed arm received continuous venovenous hemodiafiltration with a median time from stage 2 AKI to the initiation of RRT of 6 hours in the early arm compared with 25.5 hours in the delayed arm. Ninety-day all-cause mortality was 39.3% in the early therapy arm compared with 54.7% in the delayed arm ($P = .03$).

A differing view was provided by the Artificial Kidney Initiation and Kidney Injury (AKIKI) trial, a multicenter, randomized controlled trial across 31 critical care units in France. In this trial, 619 patients with stage 3 AKI who did not have emergent indications were randomized to undergo immediate initiation of RRT or a strategy of delayed initiation based on clinical indications. Of the 308 patients randomized to undergo delayed provision of RRT, only 157 (51%) ultimately required this therapy. For those patients receiving RRT, the median time from reaching stage 3 AKI to randomization was 4.3 hours in the early arm compared with 57 hours in the delayed arm. Sixty-day mortality did not differ between the 2 treatment arms (48.5% vs. 49.7%). No differences in the overall outcome were observed in important patient subgroups (septic shock and acute respiratory distress syndrome).

Another more recent trial, the Initiation of Dialysis Early versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial, had similar results to the AKIKI trial. IDEAL-ICU enrolled 488 patients with sepsis and AKI in 29 French intensive care units. Patients who did not have an emergent indication for RRT were randomized either to begin RRT within 12 hours of meeting the equivalent of stage 3 AKI or to have RRT delayed until either an emergent indication appeared or for 48 hours. Of the 246 patients randomized to early RRT, 239 initiated RRT a median of 7.6 hours after meeting criteria for stage 3 AKI, whereas 149 of the 242 patients randomized to the delayed arm initiated RRT after a median of 51.5 hours. Ninety-day mortality was unchanged between the 2 groups at 58% in the early initiation arm compared with 54% in the delayed initiation arm.

A number of important observations should be made. The key entry criterion for both the AKIKI and IDEAL-ICU trials (stage 3 AKI) was the criterion for late initiation of RRT in the ELAIN trial. In addition, both the AKIKI and IDEAL-ICU trials allowed the use of all modalities of RRT, whereas ELAIN patients received only continuous venovenous hemodiafiltration. Both AKIKI and IDEAL-ICU trials excluded patients with emergent criteria for the initiation of RRT including severe hyperkalemia or pulmonary edema, whereas the majority of patients in the ELAIN trial had fluid overload or pulmonary edema before enrollment. Although additional research is needed, it appears that in the absence of emergent indications such as severe electrolyte disorders (hyperkalemia), azotemia, severe volume overload, refractory metabolic acidosis, or dangerous toxin exposure, delayed RRT initiation is reasonable.

Summary Points

- Resuscitation fluids have typically included large amounts of chloride. As a renal vasoconstrictor, chloride is now recognized as a source of kidney injury. Both fluids used for acute resuscitation and maintenance intravenous fluid therapy should be considered as potential renal toxins. Alternative solutions with electrolyte composition approximating that in plasma should be considered for acute and maintenance fluid therapy.
- A large number of markers of renal injury are under study. These markers offer the opportunity for specific identification of cells in the kidney affected by renal insults. Newer markers of renal injury may be found both in urine and plasma and appear before changes in traditional chemistries.
- Renal injury biomarkers may ultimately be used in combination with traditional indicators of renal function such as creatinine. The combination of biomarkers and standard chemistries may reflect earlier evolution of renal cellular injury and its manifestation as reduced renal filtration function.
- A variety of renal replacement therapy options are available. In the management of critically ill patients, venous access is typically obtained with slower toxin or volume removal, which is better tolerated, particularly in the patient with hemodynamic compromise.
- Despite the long-standing availability of renal replacement technologies, the optimal timing for the initiation of renal replacement therapy remains unclear. Given uncertainty in the current literature, the clinician continues to fall back on classic indications for early renal support including volume overload, early correction of electrolyte and acid-base disturbance, toxin management, and control of acute azotemia.
- In the critical care setting, the benefits of RRT must be balanced with the risks and burdens. Complications are associated with vascular access; hypotension during renal replacement therapy, which could cause secondary kidney injury; and the burden of significant resource use to provide long intervals of RRT typically required in the critical care unit.

Acknowledgments

The authors gratefully acknowledge the assistance of Ms. Sherry Willett in preparation of this series for *Air Medical Journal*.

Anna Rauzi, BS, was a research intern, Critical Care Research Center, Regions Hospital St. Paul, MN.

David J. Dries, MSE, MD, is the chair of the department of surgery at HealthPartners Medical Group and a professor of surgery and an adjunct clinical professor of emergency medicine at the University of Minnesota in St Paul, MN, and can be reached at david.j.dries@healthpartners.com.