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Critical Care Nephrology: Acute Renal Failure in the Intensive Care Unit

By ELISABETH D. RIVIELLO, MD, and KENNETH B. CHRISTOPHER, MD

Despite technical advancements in the management of acute renal failure (ARF) over the last 50 years, critically-ill patients with ARF continue to demonstrate high mortality rates. From 1970 to 2004, the mortality of patients with ARF in the intensive care unit (ICU) remained unchanged at nearly 50%.¹ A recent prospective observational study in >29,000 ICU patients found that 5.7% developed ARF in the ICU, with septic shock a likely etiology in 47.5%. Importantly, patients who had ARF or were treated with renal replacement therapy (RRT) had an overall hospital mortality of 60.3%.² In ARF, delayed nephrology consultation is associated with increased mortality and morbidity, whether or not dialysis is ultimately required.³

The lack of progress in improving outcomes, as well as the inconclusive nature of most ARF studies, is due, at least in part, to the nature of ARF as a syndrome with multiple etiologies.⁴ Recent efforts have been made to more accurately define and classify ARF.⁵ While methods to prevent renal damage have been extensively investigated, the primary prevention strategies are still meticulous attention to volume status and circulation, coupled with avoidance of nephrotoxic agents.⁶ Similarly, while multiple pharmacologic interventions have been tested for treatment of early ARF,⁷ RRT remains the mainstay of treatment in the ICU.⁶ Our understanding of the therapeutic potential of RRT has expanded, such that RRT is now used for some non-renal indications in the setting of critically-ill patients.⁸

This issue of *Nephrology Rounds* focuses on some practical aspects of nephrology care in the ICU, namely the definition of ARF; indications for initiation of RRT; RRT parameters (including timing of therapy initiation, modality, dose, and anticoagulation); and 2 new developments that may change the way critical care nephrology is practiced – namely high volume hemofiltration and the emergence of new urinary biomarkers.

Defining acute renal failure

Although ARF in the ICU is common, carries a high risk of mortality, and has been studied for many years, its definition is not precise.⁷ A review of 28 studies of postoperative ARF found that each study used a different definition for ARF.⁹ Even the term “acute renal failure” has been called into question, as it does not reflect the frequent occurrence of renal dysfunction and injury that does not result in complete failure.¹⁰ To this end, the term “acute kidney injury” has been proposed.

A 2003 *Journal of the American Medical Association (JAMA)* review on ARF asserted that, while no consensus existed on its definition, it was reasonable to define ARF as a ≤ 2 -week increase in serum creatinine (SCr) of 0.5 mg/dL (44.2 $\mu\text{mol/L}$) for patients with baseline SCr of <2.5 mg/dL (221 $\mu\text{mol/L}$), or an increase in SCr by $>20\%$ for patients with a baseline SCr >2.5 mg/dL (221 $\mu\text{mol/L}$).¹¹ Also in 2003, Mehta and Chertow created a classification system for acute renal dysfunction with grading in each of 4 categories: predisposition to acute disease based on chronic kidney disease (CKD) and risk factors; insult (nature and timing); response based on biomarkers (SCr/glomerular filtration rate [GFR], and urine output); and later consequences (ranging from no organ failure to multiorgan failure).⁷ The goal of this classification was to allow for a more complete understanding of the severity and best course of action at each point in a patient's course, as well as more precise research categorizations.

In 2004, the Acute Dialysis Quality Initiative (ADQI) workgroup published the RIFLE criteria, an acronym for 3 levels of renal dysfunction (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function), and 2 levels of outcome (Loss of kidney function and End-stage kidney disease). The dysfunction criteria are based on a relative rise in creatinine, the absolute level of urine output, or both. The failure category has an additional means of classification, SCr ≥ 4 mg/dL, as a means to capture the severity of acute renal disease in chronic renal disease patients whose relative creatinine increase may not otherwise reflect ARF.⁵

The predictive value of RIFLE criteria for mortality was examined, with results pointing to an almost linear relationship between RIFLE severity and mortality.¹² This retrospective, single-



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center trial included 20,126 patients, and found 9.1% of all patients to be in the risk category, 5.2% in the injury category, and 3.7% in the failure category. Hospital mortality for the 3 groups was 4.4% for normal patients, 15.1% for risk patients, 29.2% for injury patients, and 41.1% for failure patients. Multivariate logistic regression analysis indicated that all RIFLE criteria were significant predictive factors for hospital mortality, with an increase in odds ratios with severity.

Indications for RRT in the ICU

Acutely ill patients have 2 potential indications for RRT: renal replacement and renal/multi-organ support.¹³ The latter may protect other organs from damage by improving the body's overall milieu (circulation, balance of inflammatory mediators, etc.) or by allowing therapies for other organ systems that the patient otherwise could not tolerate, such as volume resuscitation or aggressive nutrition.¹³

Examples of indications for renal replacement include electrolyte imbalances, acid/base disturbances, and uremic complications. Examples of indications for renal support include nutrition, congestive heart failure, treatment of respiratory acidosis in adult respiratory distress syndrome, liver failure, pancreatitis, fluid management in multi-organ failure, lactic acidosis, crush injury, tumor lysis syndrome, and potentially cytokine removal in sepsis.^{8,14} Continuous renal replacement therapy (CRRT), rather than intermittent hemodialysis (IHD) is particularly suited to many of the renal support goals, and high volume hemofiltration is a development based on CRRT that may be helpful in modifying inflammatory mediators in sepsis.^{8,14,15}

Principles of renal replacement therapy

RRT modalities are categorized by mechanisms of fluid and solute removal and by the intermittent vs. continuous nature of treatment. Given the lack of definitive outcome data for RRT modality in ARF, current practice is largely dictated by the modalities that are available at a given hospital and the personal experience of physicians.

Fluid removal – ultrafiltration: Fluid removal is accomplished through ultrafiltration (UF) in all RRT methods with the exception of peritoneal dialysis (PD). UF uses a pressure gradient to drive fluid across a semipermeable membrane. Factors affecting the UF rate are the transmembrane pressure gradient, membrane water permeability, and membrane surface area.

Solute removal: diffusion and convection: The 2 primary mechanisms of solute removal are diffusion and convection. In hemodialysis, solutes are cleared by diffusion. Diffusion is the movement of a solute from a higher to a lower concentration across a semipermeable membrane. Diffusion is most effective with small molecular weight molecules (<500 daltons). The dialysate fluid, generally containing sodium, bicarbonate, chloride, magnesium, and calcium, runs countercurrent to blood flow, thus maximizing the concentration gradient. The factors affecting the rate of solute clearance are solute molecular weight, flow rates of blood and dialysate, dialysis duration, concentration gradient across the membrane, membrane surface area, and membrane permeability.

Convection, the primary mechanism of solute clearance in hemofiltration, occurs when solutes are “dragged” with water during ultrafiltration. Solute eliminated by convection include both small molecular weight molecules, such as potassium, phosphates, creatinine, and blood urea nitrogen

(BUN), as well as medium molecular-weight molecules up to 40,000 daltons. Solute clearance is primarily dependent on the ultrafiltration rate, the ultrafiltration coefficient of the membrane, and the sieving coefficient of the solute that is inversely proportional to the molecular weight.

When to initiate RRT

Not surprisingly, just as the definition of ARF lacks full consensus, so does the criteria for when to initiate RRT in ARF. The ADQI working group, for instance, found variations of up to 2-fold in the reported levels of urine output, blood urea nitrogen, and SCr at the time of initiation of RRT.¹⁶ One retrospective study of trauma patients noted a survival advantage in patients whose CRRT was started at a lower initial level of BUN (“early starters”) vs. higher BUN (“late starters”).¹⁷ Similarly, the ADQI group notes that since the complications of chronic renal failure (CRF; eg, pulmonary edema or hyperkalemia) that conventionally lead to the initiation of therapy may have more severe consequences for critically ill patients with ARF, RRT should start prior to these complications.¹⁶ A recent review article in *The Lancet*⁶ notes the lack of objective standards for therapy initiation, but nonetheless proposes criteria for initiation in cases of oliguria, severe hyperkalemia, severe pulmonary edema, severe acidemia, gross uremia, severe sodium abnormalities, hyperthermia, and overdose (Table 1).

RRT modalities

The main intermittent modalities are IHD and sustained low-efficiency dialysis (SLED), also referred to as extended daily dialysis (EDD). The continuous modalities are PD and CRRT, which exists in various forms using ultrafiltration, hemodialysis, hemofiltration, hemodiafiltration, and combinations of these.

The 3 primary modalities of RRT in ARF are IHD, CRRT, and SLED (Table 2). PD, a common modality in CRF, is generally not used in the acute setting as it carries an increased risk of peritonitis, cannot be used in patients with recent abdominal surgery or abdominal sepsis, gives insufficient solute clearance in catabolic patients, and reduces respiratory function through impedence of diaphragmatic excursion. **Intermittent hemodialysis:** IHD uses diffusion for solute removal and ultrafiltration for volume removal. In ARF, it is generally performed 3 to 4 times per week, around 4 hours per session, with blood flow rates of 200-300 ml/min and dialysate flow rates of 500-800 mL/min.¹⁸ The advantages of IHD include swift solute and volume removal, relatively low cost and complexity, and relatively small anticoagulation requirements compared with other modalities due to rapid flow rates. Its primary disadvantage is the risk of hypotension, such that 10% of ARF patients cannot tolerate IHD due to hemodynamic instability.¹⁸ In addition, the rapid movement of solutes to the extravascular space can cause cerebral edema, making this modality contraindicated in patients with head trauma or hepatic encephalopathy.

Continuous renal replacement therapies: CRRT includes a variety of modalities that use ultrafiltration and may use convection, diffusion, or both. Treatment is 24 hours per day with a blood flow of 100-200 ml/min, and a dialysate flow of 17-34 ml/min in the case of diffusive technologies.¹⁸ The advantages of CRRT stem from its continuous nature: both fluid and solutes shift more slowly, allowing for better hemodynamic stability and more precise solute concentration

Table 1: Proposed criteria for initiation of renal replacement therapy in critically ill patients with acute renal failure⁶

- Oliguria: urine output <200 mL in 12 h
- Anuria: urine output <50 mL in 12 h
- Hyperkalemia: potassium concentration >6.5 mmol/L
- Severe acidemia: pH <7.0
- Azotemia: urea concentration >85 mg/dL
- Uremic encephalopathy
- Uremic neuropathy/myopathy
- Uremic pericarditis
- Plasma sodium abnormalities: concentration >155 mmol/L or <120 mmol/L
- Hyperthermia
- Drug overdose with dialyzable toxin

control. The gradual nature of solute removal in CRRT makes it less likely to cause cerebral edema.¹⁹ In addition, CRRT has greater cumulative solute removal than IHD due to the longer treatment time.

It has been postulated that the removal of middle molecular weight (MMW) molecules, including pro-inflammatory molecules with CRRT may be advantageous in sepsis; however, CRRT may also remove anti-inflammatory molecules. Therefore, the net effect is dependent on the balance of pro-inflammatory and anti-inflammatory molecules that are removed. The benefit of removing inflammatory molecules via CRRT has not been demonstrated.¹⁶

Replacement solution replaces the ultrafiltrate continuously removed by hemofiltration and hemodiafiltration. Buffers used in the replacement solution include lactate, bicarbonate, or citrate. Lactate and citrate are metabolized by the liver and muscles to produce bicarbonate, which is easily tolerated, but can be unstable in solution. Commercially-available bicarbonate solutions are manufactured with a 2-compartment bag to prevent carbonate precipitation during storage. Lactate is stable in replacement solution; however, it may contribute to an existing lactic acidosis in patients with sepsis or liver failure.²⁰ Citrate provides regional anticoagulation of the hemofilter. The choice of parameters within CVVH offers some flexibility for patients with differing underlying processes.⁸ Citrate is successfully used in patients at risk of bleeding, while bicarbonate-based replacement solution is preferred in those with lactic acidosis or liver failure.²¹

Slow low-efficiency dialysis/extended daily dialysis: SLED, sometimes referred to as EDD, can use the same hemodialysis machines as IHD, but runs for longer periods at slower rates. A usual treatment runs for 6-12 hours, with blood flow rate of 200 ml/min and dialysate flow rate of 300 ml/min. It combines many of the advantages of IHD and CRRT. It is relatively low cost and low complexity since it uses the same technology as IHD; however, it also has the advantages of gradual fluid and solute removal and high total solute removal. In addition, because it is lengthy, but not continuous, it allows for scheduling of other diagnostic and therapeutic procedures between treatments.

Although the beginnings of dialysis are rooted in SLED, its regular use in the ICU is a relatively new phenomenon. Some small studies have indicated that it is a safe and effective alternative to CRRT in the setting of ARF in the ICU,²² but large randomized trials comparing its outcomes to IHD and CRRT have not been performed. Variations on SLED have

Table 2: Features of IHD, CRRT, and SLED/EDD in Acute Renal Failure

	IHD	CRRT	SLED
Fluid shift mechanism	Ultrafiltration	Ultrafiltration	Ultrafiltration
Solute shift mechanism	Diffusion	Diffusion, convection, or both	Diffusion
Blood flow rate	≥200 ml/min	< 200 ml/min	200 ml/min
Dialysate flow rate	≥500 ml/min	17-34 ml/min	300 ml/min
Duration	3-4 hours	24 hours/day	6-12 hours
Advantages/special uses			
• Rapid fluid removal	✓		
• Rapid solute clearance	✓		
• Severe hyperkalemia	✓		
• Hemodynamic instability		✓	✓
• Better fluid control		✓	✓
• High nutritional support		✓	?
• Removal of middle-molecular weight solutes		✓	

been tried, including nocturnal therapy to maximize time for other therapeutic and diagnostic procedures, and sustained low efficiency dialysis (SLEDD-f), which combines diffusion and convection.

RRT modalities and outcomes

Data comparing the outcomes of different modalities in ARF continues to be inconclusive, although what is available points to similar survival rates for IHD and CRRT. Older studies suffer from inadequate study designs and the use of older technologies, including arteriovenous access. The most recent data are discussed below.

In 2001, Mehta et al performed a multicenter, randomized, controlled trial comparing IHD with CRRT in 166 ICU patients. The study revealed no survival advantage for CRRT over IHD; however, unexpected differences in the randomized arms precluded a meaningful direct analysis.²³ An extensive meta-analysis by Kellum et al in 2002 revealed no differences in mortality for CRRT vs. IHD after examining 13 studies comprising 1400 patients (RR 0.93; CI, 0.79-1.09, $p=0.29$). However, when controlling for disease severity and study quality, there was a survival advantage with CRRT (RR 0.72; CI, 0.60-0.87, $p<0.01$). The authors concluded that the data were insufficient to make strong recommendations for CRRT in ARF.²⁴ A meta-analysis in 2002 found no differences in mortality between IHD and CRRT (IHD vs. CRRT, RR 0.96; CI, 0.85- 1.08; $p =0.50$).²⁵ Trials conducted since these meta-analyses were performed fail to definitively answer the question of whether dialysis modality affects mortality and renal recovery outcomes. Small retrospective studies and recent small randomized prospective trials have all failed to show any survival advantage with the use of CRRT.²⁶⁻²⁸ Overall, these studies suggest a lack of survival improvement with CRRT versus IHD, with a possibility of improvement with CRRT in the most severely ill ARF patients.

While studies have failed to show a survival advantage for any of the modalities, there are specific conditions where a particular RRT method is preferred over another. CRRT is recommended in patients with cerebral edema or liver failure,

while IHD is more appropriate in patients with an increased risk of bleeding⁶ and life-threatening hyperkalemia. Despite the lack of a clear survival advantage, CCRT allows for precise adaptable volume control over time and is thus a powerful tool in managing hemodynamically unstable patients with volume overload with and without ARF.

RRT dose

While standard dosing targets in ESRD have been developed, dosing targets in ARF are not clear. Urea kinetic modeling is the basis for ESRD dosing, but several of its baseline assumptions are not valid in ARF; eg, urea is not in steady state during the hypercatabolism of acute severe illness, total body water and volume of distribution of urea are variable, and access recirculation may occur.²⁹ In addition, it may be that clearance of MMW molecules is more relevant than urea clearance in critical illness. Suggestions have been made (eg, increasing conventional estimates of total body water by a factor of 1.2, and targeting a time-averaged blood urea nitrogen level of <60 mg/dL with IHD),²⁹ but no consensus exists.

Schiffel et al performed a prospective trial in 160 patients enrolled in an alternating fashion and found better uremia control, fewer hypotensive episodes, faster resolution of ARF, and lower mortality among those receiving daily IHD treatments versus alternate-day treatments (28% versus 46%; $p=0.01$).³⁰ Similarly, Ronco et al demonstrated a benefit with higher doses of CRRT. Ronco randomly assigned 425 ARF patients to receive ultrafiltration at 20 mL/h/kg, 35 mL/h/kg, or 45 mL/h/kg. Survival was significantly higher in the 35 and 45 mL/h/kg groups, in comparison to the 20 mL/h/kg group ($p=0.0007$ and $p=0.0013$, respectively).³¹ However, Bouman et al found no significant survival differences between high-volume hemofiltration and low-volume hemofiltration in a randomized controlled trial of 106 patients.³² However, questions remain about sample size and methodology in these studies that leave the issue of optimal dose unclear.

The VA/NIH Acute Renal Failure Trial Network (ATN) Study is designed to clarify the optimal dose of RRT in critically-ill patients with ARF. It is a multicenter, prospective, randomized, parallel-group trial of high-intensity versus low-intensity RRT in critically ill patients. Its primary study endpoint is 60-day all-cause mortality. Secondary endpoints include all-cause hospital mortality, 1-year mortality, and recovery of renal function by day 28.³³ The trial is designed to allow patients to receive both CRRT and/or IHD, depending on changes in hemodynamic stability over time. It is possible that higher-dose therapy will be beneficial due to better control of uremia, better hemodynamic control with less ischemia and, possibly, a decrease in inflammatory mediators.^{18,34,35}

Anticoagulation in CRRT

The primary disadvantage of CRRT is the need for continuous heparin anticoagulation to delay hemofilter clotting and the resulting increased risk of bleeding complications. Multiple methods have been tried to

overcome this problem, including regional anticoagulation with a protamine-heparin combination, prostaglandins, Factor Xa inhibitor fondaparinux, direct thrombin inhibitors, including bivalirudin, argatroban, and dermatan sulfate, the protease inhibitor nafamostat, the addition of heparin to priming fluid, intermittent saline flushing, albumin priming, increasing blood flow, divided heparin administration, and use of flat-plate filters.³⁶

The alternative method – with the most evidence for efficacy and safety – is regional citrate anticoagulation that allows for prolongation of filter life without the use of heparin. It entails a pre-filter infusion of citrate and works by extracorporeal chelation of calcium ions to decrease their availability for calcium-dependent steps in the clotting cascade. Systemic anticoagulation does not occur as the ionized calcium level is restored when blood returning from the extracorporeal system is mixed with venous blood. Rapid metabolism of citrate by the kidney, liver, and muscle, restores bicarbonate levels and releases calcium.³⁶ However, patients with severe liver failure and lactic acidosis may have difficulty in metabolizing citrate and develop citrate toxicity. Citrate toxicity is characterized as low ionized calcium, elevated total serum calcium, exacerbation of serum acidosis, and an elevation of the anion gap.

A systematic review of studies through June 2005 concluded that, although available data quality is poor, it appears that, compared with heparin, anticoagulation with citrate provides better circuit survival time, less bleeding, and some evidence for improved biocompatibility by decreasing activation of coagulation and leukocytes.³⁶ Two prospective observational trials confirm the trend toward decreased bleeding, although a study in pediatric patients did not demonstrate a benefit in filter clotting time.^{37,38}

Citrate anticoagulation can add complexity to CRRT due to requirements for customized dialysate solutions or replacement fluids and frequent laboratory monitoring, including electrolytes, ionized Ca, and acid/base status.^{18,36} Nonetheless, it is a powerful method for increasing the safety and efficacy of CRRT in ARF. Citrate can cause particular metabolic complications, especially in patients with liver dysfunction and decreased citrate metabolism; however, these generally are not life-threatening and are easily corrected. In addition, recently available commercial citrate solutions may increase the feasibility of citrate for widespread use and techniques for simpler CRRT protocols are continually being developed and tested.³⁹

New developments in the treatment of ARF

High volume hemofiltration (HVHF) for sepsis/SIRS/MODS

Multiple organ dysfunction syndrome (MODS), generally caused by severe sepsis and septic shock, is the most frequent cause of mortality in the ICU. Most patients with ARF in the ICU have MODS and conceptions about RRT have evolved from the treatment of renal dysfunction alone to the treatment of MODS.⁴⁰ It has been postulated that removal of MMW molecules, including pro-inflammatory molecules with CRRT, may be advantageous in sepsis. However, CRRT may also

remove anti-inflammatory molecules, so that the net effect is dependent on the balance of pro-inflammatory and anti-inflammatory molecules removed. The benefit of removing inflammatory molecules via CRRT has not been demonstrated.¹⁶

HVHF is an emerging technique that uses specialized CRRT equipment to treat MODS. The condition is associated with a loss of autoregulation of pro- and anti-inflammatory mediators that leads to both “hyperinflammation” and “immunodepression.”⁴¹ Increased clearance of MMW and high molecular weight solutes that make up the inflammatory mediators can be achieved with a high-volume approach.⁴² While drug treatments that block a specific mediator have not proved effective, it is postulated that the generalized and non-specific removal of solutes through HVHF may disrupt the escalation of inflammatory mediators. This theory is described by the “peak concentration hypothesis,” the concept that reducing the peaks of soluble mediators by using continuous hemofiltration may interrupt the damaging pro- and anti-inflammatory processes.⁴³

Preliminary evidence suggests that HVHF may be effective in septic patients.⁴⁴ The 45 ml/kg/hr ultrafiltration dose studied by Ronco³¹ is classified as HVHF by ADQI standards⁴⁵ and the nonsignificant trend toward improved survival in Ronco’s study with the higher HVHF dose is cited as evidence that there may be a “sepsis dose” of CVVH that is greater than the “renal dose” used for non-septic patients.⁴⁴

Thus far, small and mostly non-randomized studies have pointed to a possible benefit of HVHF in MODS. Piccinni et al analyzed outcomes in 80 patients with septic shock, acute lung injury, and oliguric acute renal injury in an 8-year retrospective analysis before, and after, the introduction of a septic shock protocol with early isovolemic hemofiltration (EIHf).⁴⁶ This consisted of EIHf at 45 ml/kg/h of plasma-water exchange over 6 hours, followed by CVVH. The study found EIHf to be associated with improved gas exchange, hemodynamics, greater likelihood of successful weaning, and greater 28-day survival (55% survival for conventionally-treated versus 27.5% for patients receiving EIHf, $p < 0.05$). Despite selection bias and improved care over the trial time, the findings are suggestive of a benefit with HVHF.

Blood purification strategies in general, and HVHF in particular, are still in their early stages. Machines with a capacity for increased blood flow and increased filter surface area are required,⁴⁶ although some machines that can safely perform HVHF are now available.⁴³ Consensus exists that a large randomized controlled trial is needed to study the potential benefit of HVHF.

Renoprotection and biomarkers

Most study designs evaluating renoprotective agents in patients who develop acute tubular necrosis begin therapy after SCr has risen. Due to the lack of reliable biomarkers that may detect tubular injury prior to SCr elevation, renoprotective agents are usually given 48-72 hours following the initial insult. Therefore, patients often have perfusion deficits and volume deficits corrected prior to administration of such agents. In human trials, no agent has consistently been demonstrated to

produce positive outcomes in early treatment, including loop and osmotic diuretics, “low-dose” dopamine, insulin-like growth factor-1, endothelin receptor antagonists, and atrial natriuretic peptide.⁷ A single-center, randomized, controlled trial evaluating intensive insulin therapy in postoperative mechanically-ventilated patients did demonstrate a significant decrease in the incidence of ARF requiring dialysis.⁴⁷

Conventional SCr, BUN and urinary markers (eg, fractional excretion of Na, cast morphology) of renal dysfunction are poor indicators of acute kidney injury.⁴⁸ Novel urinary protein biomarkers under investigation include kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), urine sodium/hydrogen exchanger isoform 3 (NHE3), urinary cytokines, urinary cysteine-rich protein 61, urinary actin, urinary glutathione-S-transferase (GSTs), serum and urine cystatin C.⁴⁹ Urinary KIM-1 levels are significantly higher in patients with ischemic ATN compared to those in patients with other forms of ARF and chronic renal failure.⁵⁰ Patients with ATN also have significantly greater median urinary IL-18 concentrations than those with other forms of renal failure.⁵¹ Levels of urinary NHE3 are increased in patients with prerenal azotemia and in patients with ATN with NHE3 being 6-fold higher than in prerenal azotemia.⁵² In pediatric cardiac surgery patients, the finding of NGAL in the urine 2 hours following cardiopulmonary bypass is a powerful independent predictor of acute renal injury.⁵³ The early identification of proteins in the urine coincidental with ARF may allow for earlier recognition of ARF prior to the rise in SCr. In addition, the use of urinary biomarkers may distinguish renal tubules at risk prior to significant injury. Urinary markers may ultimately allow for better titration of diuretics and avoidance of cumulative nephrotoxicity. Earlier recognition of ARF by urinary biomarkers may also be important in the study of future renoprotective agents given earlier in the course of ARF.

Conclusion

Acute kidney injury in critically-ill patients is a syndrome that is only recently being consistently defined and classified. It continues to carry a high mortality rate, even with advances in technology. Agents for preventing and treating acute renal injury have been disappointing and renal replacement therapy continues to be the primary therapeutic approach. Options for RRT modalities include IHD, CRRT, and SLED. Within these modalities, choices about the timing of therapy initiation, dosage, membrane choice, and anticoagulation therapy need to be made, although scant evidence is available to guide these decisions. The VA/NIH Acute Renal Failure Trial Network Study should provide new data about dosing decisions. While no modality has been shown to produce better outcomes, certain patient characteristics, such as hemodynamic status, may point to the use of one over another. In addition, RRT is being increasingly used for renal support in multiple organ failure. HVHF is a new application of RRT that may alter the disequilibrium of inflammatory mediators in sepsis and SIRS. The emergence of new biomarkers may allow for earlier, more sensitive, and more specific diagnosis of acute renal injury, with the potential for earlier and more efficacious therapy.

Elisabeth D. Riviello, MD, is a Medical Scholar, Medical Scholars Program, Vanderbilt University School of Medicine.

Kenneth Christopher, MD, is an Instructor of Medicine, Harvard Medical School, and Associate Physician, Brigham and Women's Hospital.

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