Acute kidney injury in the intensive care unit: An update and primer for the intensivist

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Objective: **Acute kidney injury is common in critically ill patients and is associated with significant morbidity and mortality. Patients across the spectrum of critical illness have acute kidney injury. This requires clinicians from across disciplines to be familiar with recent advances in definitions, diagnosis, prevention, and management of acute kidney injury in the intensive care unit. The purpose of this concise review, therefore, is to address, for the non-nephrologist, clinically relevant topical questions regarding acute kidney injury in the intensive care unit.**

Data Sources: **The authors (nephrologists and intensivists) performed a directed review of PubMed to evaluate topics including the definition, diagnosis, prevention, and treatment of acute kidney injury in the intensive care unit. The goal of this review is to address topics important to the practicing intensivist.**

Data Synthesis and Findings: **Whenever available, preferential consideration was given to randomized controlled trials. In the absence of randomized trials, observational and retrospective studies and consensus opinions were included.**

Conclusions: **Acute kidney injury in the intensive care unit is a clinically relevant problem requiring awareness and expertise among physicians from a wide variety of fields. Although many questions remain controversial and without definitive answers, a periodic update of this rapidly evolving field provides a framework for understanding and managing acute kidney injury in the intensive care unit. (Crit Care Med 2010; 38:261–275)**

Key Words: acute kidney injury; intensive care unit

Acute kidney injury (AKI), previously termed acute renal failure, refers to a sudden decline in kidney function causing disturbances in fluid, electrolyte, and acid–base balance because of a loss in small solute clearance and decreased glomerular filtration rate (GFR). The nomenclature shift to AKI more accurately represents the spectrum of disease from subclinical injury to complete organ failure. This review focuses on key questions for the intensivist faced with AKI in the intensive care unit (ICU).

Epidemiology of AKI in the ICU

AKI in the ICU is common, increasing in incidence (1–4), and is associated with a substantial increase in morbidity and mortality (5, 6). AKI occurs in approximately 7% of all hospitalized patients (7) and in up to 36% to 67% of critically ill patients depending on the definition used (6, 8–11). Based on >75,000 critically ill adults, more severe AKI occurs in 4% to 25% of all ICU admissions (6, 8, 9, 11). On average, 5% to 6% of ICU patients with AKI require renal replacement therapy (RRT) (6, 8–11).

Reported mortality in ICU patients with AKI varies considerably between studies depending on AKI definition and the patient population studied (e.g., sepsis, trauma, cardiothoracic surgery, or contrast nephropathy). In the majority of studies, mortality increases proportionately with increasing severity of AKI (6, 10–13). In patients with severe AKI requiring RRT, mortality is approximately 50% to 70% (9, 14–16). While AKI requiring RRT in the ICU is a well-recognized independent risk factor for in-hospital mortality (17), even small changes in serum creatinine (SCr) are associated with increased mortality (18–21). Notably, multiple studies of patients with AKI and sepsis (22–24), mechanical ventilation (25), major trauma (26, 27), cardiopulmonary bypass (17, 28–30), and burn injuries (31) have consistently demonstrated an increased risk of death despite adjustment for comorbidities and severity of illness.

Morbidity, a less appreciated consequence of AKI in the ICU, is associated with increased cost (18), increased length of stay (6, 14, 18, 26), and increased risk of chronic kidney disease (CKD), including end-stage kidney disease (9, 15, 16, 32–37). The true incidence of CKD after AKI is unknown because epidemiologic studies do not routinely or consistently report rates of renal recovery and those that do use variable definitions (38).

Definition of AKI in the ICU

More than 35 definitions of AKI currently exist in the literature (39). The Acute Dialysis Quality Initiative convened in 2002 and proposed the RIFLE classification (risk, injury, failure, loss, end-stage kidney disease) specifically for AKI in critically ill patients (Table 1) (40). Using SCr and urine output, the RIFLE criteria define three grades of severity and two outcome classes. The most severe classification met by either criterion should be used. Of note, patients with primary kidney diseases such as glomerulonephritis were excluded from this definition.

More recently the Acute Kidney Injury Network (AKIN), an international multidisciplinary organization composed of

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Table 1. Classification/staging systems for acute kidney injury

	RIFLE	SCr Criteria	UOP Criteria	AKIN Stage	SCr Criteria	UOP Criteria
Increasing Severity of AKI	R	↑ SCr × 1.5	<0.5 mL/kg/hr × 6 hrs	1	↑ in SCr ≥0.3 mg/dL or ↑ ≥150% to 200% from baseline (1.5- to 2-fold)	<0.5 mL/kg/hr for >8 hrs
	I	↑ SCr × 2	<0.5 mL/kg/hr × 12 hrs	2	↑ in SCr to >200% to 300% from baseline (>2- to 3-fold)	<0.5 mL/kg/hr for >12 hrs
	F	↑ SCr × 3, or SCr ≥4 mg/dL with an acute rise of at least 0.5 mg/dL	<0.5 mL/kg/hr × 24 hrs or anuria × 12 hrs	3	↑ in SCr to >300% (3-fold) from baseline or SCr ≥4 mg/dL with an acute rise of at least 0.5 mg/dL	<0.5 mL/kg/hr × 24 hrs or anuria × 12 hrs
	L	Persistent loss of kidney function for >4 wks				
	E	Persistent loss of kidney function for >3 months				

RIFLE, risk, injury, failure, loss, end-stage kidney disease; AKIN, acute kidney injury network; SCr, serum creatinine; UOP, urine output. RIFLE criteria adapted from Bellomo et al (40). AKIN criteria adapted from Mehta et al (42).

nephrologists and intensivists, further modified the RIFLE criteria recognizing that even very small changes in SCr (≥0.3 mg/dL) adversely impact clinical outcome (6, 7, 10, 11, 19, 21, 41). According to AKIN, the most current consensus diagnostic criteria for AKI is "an abrupt (within 48 hrs) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL (≥26.4 μmol/L), a percentage increase in serum creatinine of ≥50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of <0.5 mL/kg/hr for >6 hrs)" (42). Importantly, the AKIN definition and classification system incorporates creatinine, urine output, and time (Table 1). Both the RIFLE and AKIN criteria were developed to facilitate clinical investigation and comparison across study populations. Epidemiologic data comparing the RIFLE and AKIN criteria have demonstrated concordance in critically ill patients (43, 44).

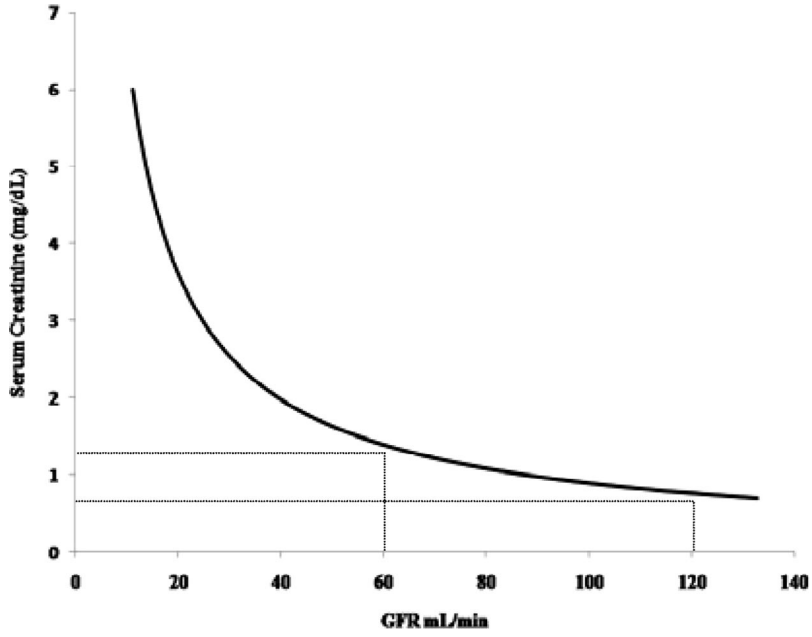

Figure 1. Relationship between glomerular filtration rate (*GFR*) and serum creatinine (*SCr*). Large changes in GFR (e.g., 50% decrease from 120 mL/min to 60 mL/min) are reflected in only small changes in SCr (0.7 mg/dL to 1.2 mg/dL).

Diagnosis of AKI in the ICU

Traditional tools to diagnose AKI (SCr) and determine etiology of AKI (clinical history, physical examination, renal ultrasound, fractional excretion of sodium [FeNa], fractional excretion of urea, blood urea nitrogen [BUN], and urine microscopy) remain the cornerstone of diagnostic tools available to the clinician in the ICU. The use of SCr to estimate GFR is limited, however, by the lack of steady-state conditions in critically ill patients. Determinants of the SCr (rate of production, apparent volume of distribution, and rate of elimination) are variable in the ICU setting (6, 8–11, 45, 46). Medications (e.g., trimethoprim, cimetidine) impair creatinine secretion and therefore may cause increases in SCr without reflecting a true decrease in GFR. Finally, SCr lacks sensitivity and underestimates the degree of kidney dysfunction in a critically ill patient. Increases in SCr substantially lag behind a reduction in GFR (Fig. 1) and thus do not provide a useful real-time assessment of GFR.

AKI spans the continuum from prerenal azotemia to acute tubular necrosis, from functional to structural injury. Efforts to differentiate between these two entities have classically included FeNa and urine microscopy. Urine microscopy can be helpful in differential diagnosis (e.g., granular casts and renal tubular epithelial cells in acute tubular necrosis, cellular casts in glomerular injury, eosinophiluria in acute interstitial nephritis, or atheroembolic AKI). Of clinical note, nephrologist review of urine microscopy

has been demonstrated to be superior to clinical laboratory interpretation (47). Using a proposed scoring system, microscopic examination of the urine sediment is a highly predictive method for differentiating prerenal azotemia from acute tubular necrosis (48). However, the presence of muddy brown casts and renal tubular epithelial cells are usually seen relatively late and thus are not sensitive for early detection of AKI (49, 50). FeNa is frequently useful for differentiating "prerenal" (diminished renal perfusion, FeNa $<1\%$) from "intra-renal" (ischemia or nephrotoxins, FeNa $>2\%$) (50, 51). Urine microscopy and FeNa can be valuable tools in determining the cause of AKI but have no current role in early detection or diagnosis of AKI. Furthermore, "prerenal" and "intra-renal" causes of AKI commonly coexist in the ICU patient.

Prerenal azotemia, in the absence of validated new diagnostic biomarkers, often remains a retrospective diagnosis, made only after response to a volume challenge. Whereas it is important to appropriately identify and treat prerenal azotemia, fluid administration is not without consequence in the critically ill patient. A complete assessment of the patient's overall volume status is pivotal before aggressive resuscitative efforts to enhance renal perfusion. This is of particular importance considering data demonstrating adverse effects of volume overload in critically ill patients (52, 53). Because of the limitations of traditional tools, novel candidate biomarkers of AKI (discussed separately) are being actively investigated.

Common Causes of AKI in the ICU

The cause of AKI in the ICU is commonly "multi-factorial" and frequently develops from a combination of hypovolemia, sepsis, medications, and hemodynamic perturbations (Table 2). It is frequently not possible to isolate a single cause, thereby further complicating the search for effective interventions in this complex disease process. The pathophysiology of AKI varies according to the underlying etiology and is beyond the scope of this article.

Sepsis is the most common cause of AKI in a general ICU, accounting for up to 50% of cases (6, 8–11, 23, 45, 54). AKI is common after cardiac surgery, occurring in up to 42% of patients without pre-existing kidney disease, and is associated with increased morbidity and mortality with elevations in SCr as small as 0.3 mg/dL (19). Trauma associated AKI is multi-factorial (e.g., hemorrhagic shock, abdominal compartment syndrome, rhabdomyolysis) and occurs in up to 31% of adult trauma patients (55). The kidneys are early sensors of intra-abdominal hypertension and abdominal compartment pressures $\geq$12 mm Hg may be associated with AKI (56). A sustained intra-abdominal pressure $>$20 mm Hg in association with new organ dysfunction will be associated with AKI in $>30\%$ of cases (57, 58). Rhabdomyolysis accounts for 28% of trauma-associated AKI requiring dialysis (59).

Medications are a common cause of AKI and, according to Uchino et al (9), account for nearly 20% of all cases of AKI in the ICU. The mechanism of medication induced AKI is variable and includes acute interstitial nephritis, direct tubular toxicity (e.g., aminoglycosides), and hemodynamic perturbations (e.g., nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors). Acute interstitial nephritis is likely an under-recognized etiology of medication-associated AKI in the ICU because of the relative paucity of clinical findings and need for high index of suspicion. Table 3 lists common nephrotoxins encountered in the care of critically ill patients.

Table 2. Common causes of AKI in the ICU

Five Most Common Causes of AKI in the ICU[a]
• Sepsis (most common)
• Major surgery
• Low cardiac output
• Hypovolemia
• Medications
Other Common Causes of AKI in the ICU
• Hepatorenal syndrome
• Trauma
• Cardiopulmonary bypass
• Abdominal compartment syndrome
• Rhabdomyolysis
• Obstruction

[a]The five most common causes of acute kidney injury (AKI) in the intensive care unit (ICU) based on nearly 30,000 patients (9).

Table 3. Common nephrotoxins that cause acute kidney injury in intensive care unit patients

Exogenous
• Medications
—NSAIDS
—Antimicrobials
–Aminoglycosides
–Amphotericin
–Penicillins[a]
–Acyclovir[b]
—Chemotherapeutic agents
• Radiocontrast dye
• Ingestions
—Ethylene glycol
Endogenous
• Rhabdomyolysis
• Hemolysis (HUS/TTP)
• Tumor lysis syndrome

NSAIDS, non-steroidal anti-inflammatory drugs; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

[a]Acute interstitial nephritis (AIN); [b]crystal nephropathy.

Prevention and Management of AKI in the ICU

Primary prevention of AKI in the ICU is limited to those conditions in which the timing of injury is predictable, such as exposure to radiocontrast dye, cardiopulmonary bypass, large-volume paracentesis in a cirrhotic patient, or chemotherapy. In contrast to most cases of community-acquired AKI, nearly all cases of ICU-associated AKI result from more than a single insult (6, 8–11, 45, 50, 60, 61). In the critically ill patient, the first kidney insult is often not predictable. Therefore, prevention of AKI in the ICU often means prevention of a secondary insult in an "at-risk" patient. For example, in a retrospective study of $>$5000 ICU patients, 67% of patients had AKI develop, and 45% of AKI occurred after ICU admission (6). It is in these patients that there is a potential role for prevention.

General principles of "secondary" AKI prevention include: (1) recognition of underlying risk factors that predispose patients to AKI (e.g., diabetes, chronic kidney disease, age, hypertension, cardiac or liver dysfunction); and (2) maintenance of renal perfusion, avoidance of hyperglycemia, and avoidance of nephrotoxins in these high-risk patients. Specific clinical situations in which there is evidence for preventive strategies (e.g., contrast exposure, hepatorenal syndrome [HRS]) are discussed.

Preventing Contrast-Induced Nephropathy. The primary strategies for contrast-induced nephropathy (CIN) prevention include hydration, N-acetylcysteine (NAC), and use of low-volume nonionic low-osmolar or iso-osmolar contrast. No strategy has been effective in completely preventing CIN. Risk factors for CIN include diabetes, CKD, hypotension, effective or true volume depletion (including cirrhosis and congestive heart failure), and concurrent use of nephrotoxic med-

ications. Critically ill patients intuitively represent a patient population at high risk for CIN given frequent hemodynamic instability, multiple organ dysfunction, use of nephrotoxic medications, and multiple underlying comorbidities (e.g., diabetes, CKD). However, despite the large number of randomized controlled trials (RCT) published on prevention strategies for CIN, there has been only one RCT performed specifically in critically ill adults (111). The true incidence of and risk for CIN in critically ill patients is thus unknown.

Adequate volume expression is a well-established measure to decrease the risk of CIN, whereas the choice of fluid remains controversial. Trials comparing the use of sodium bicarbonate and sodium chloride for the prevention of CIN have yielded conflicting results. Five meta-analyses of sodium bicarbonate suggest a beneficial role of isotonic sodium bicarbonate over isotonic saline (112–116); however, there is considerable heterogeneity and some publication bias confounding these findings. The most recent RCT of bicarbonate vs. normal saline showed no difference in the primary outcome of ≥25% decrement in GFR within 4 days (117). Based on currently available evidence, there is a strong suggestion that sodium bicarbonate may be superior to isotonic saline to decrease the risk of CIN.

NAC is a free radical scavenger shown to decrease the risk of CIN compared to placebo (118). Since 2003, >10 meta-analyses published on the role of NAC in CIN have yielded conflicting results likely attributable, in part, to heterogeneity in patient populations. In a recent meta-analysis of 41 studies, NAC plus saline reduced the risk for CIN more effectively than saline alone (119). A previous meta-analysis in 2007 by Gonzales et al (120) did not support the efficacy of NAC to prevent or decrease the risk of CIN. Furthermore, there are conflicting data as to whether NAC, itself, may decrease SCr measurement without affecting GFR (121, 122).

Low-volume nonionic low-osmolar or iso-osmolar contrast preparations are clearly associated with a decrease in CIN when compared to high osmolar agents. The data regarding nonionic low-osmolar contrast media vs. iso-osmolar contrast media (currently only iodixanol) is controversial. Two meta-analyses report conflicting results (123, 124). McCullough et al (123) found that use of iso-osmolar contrast media resulted in a lower incidence of CIN when compared to low-osmolar contrast media. However, Heinrich et al (124), in the most recent meta-analysis, reported no significant difference between the two unless the low-osmolar contrast media was iohexol, suggesting that all low-osmolar contrast media preparations may not be the same.

Both small observational and prospective studies have shown an increase in the risk of CIN with peri-procedural use of angiotensin-converting enzyme inhibitors (125–127). However, a recent randomized prospective trial performed in stable outpatients did not show any difference in incidence of CIN between patients who did or did not discontinue angiotensin-converting enzyme inhibitors or angiotensin receptor blockers before contrast (128). Angiotensin-converting enzyme inhibitors have not been prospectively studied in the critically ill. Therefore, although there is currently insufficient evidence to support discontinuation of these medications in critically ill adults, further study is warranted given the widespread use of these agents in clinical practice.

Whereas the use of peri-procedural hemofiltration in patients undergoing percutaneous coronary intervention was shown, in two studies, to decrease the risk of AKI (5% vs. 50%; $p = .0001$) (129, 130), this has not been widely adopted into clinical practice. In a systematic review of extracorporeal therapies for prevention of CIN, analysis of the hemodialysis studies alone (including five RCT), there was no benefit of hemodialysis and, in fact, there was a trend favoring standard therapy compared to prophylactic hemodialysis (131). A subsequent RCT of prophylactic hemodialysis in 82 patients with advanced CKD (baseline SCr 4.9 mg/dL) demonstrated improved outcomes (shorter length of stay and lower rate of long-term dialysis dependence after hospital discharge) with prophylactic hemodialysis (132). A critical limitation of all of these studies is that the clinical end point SCr was directly impacted by the intervention itself (hemofiltration or hemodialysis).

Fenoldopam and theophylline are two additional agents that have been considered for their potential role in the prevention of CIN. None of the four RCT comparing fenoldopam to either saline alone (133, 134) or NAC (135, 136) demonstrated any beneficial effect in the prevention of CIN. The role of theophylline for CIN prevention is inconsistent across studies. Although two meta-analyses suggest that prophylactic theophylline may provide some benefit, the studies were performed in primarily low-risk patients, and clinically relevant outcomes were not consistently reported (137, 138). Therefore, we cannot currently recommend the use of theophylline for prevention of CIN in critically ill patients.

The majority of these studies were not performed in critically ill patients and therefore provide no definitive guidance as to how the risk of CIN in the critically ill should be ameliorated. Because of the absence of sufficient data in the patient population of interest, clinicians must extrapolate from the best available evidence from other patient populations. Therefore, our recommendations include: (1) avoid use of intravenous contrast in high-risk patients if alterative imaging techniques are available; (2) use preexposure volume expansion using either bicarbonate or isotonic saline; (3) although of questionable benefit, use of NAC is safe, inexpensive, and may decrease risk of AKI; (4) avoid concomitant use of nephrotoxic medications if possible; and (5) use low-volume low-osmolar or iso-osmolar contrast. Future studies are needed to determine the true role of these preventive measures in critically ill patients.

Preventing AKI in Hepatic Dysfunction. AKI is a common complication of critically ill patients with hepatic failure. Pentoxifylline decreases the incidence of AKI attributable to HRS in acute alcoholic hepatitis (139). Use of intravenous albumin in patients with cirrhosis and spontaneous bacterial peritonitis significantly reduces both the incidence of AKI (33% to 10%) and mortality (41% to 22%) (140). Albumin decreases the incidence of AKI after large-volume paracentesis (141), and when used in combination with splanchnic vasoconstricting agents (e.g., terlipressin) may decrease mortality in HRS (142, 143). However, definitive therapy for AKI as a consequence of HRS remains liver transplantation in appropriate candidates. Five randomized trials of vasoconstricting agents (terlipressin or noradrenalin) plus albumin in the treatment of HRS all demonstrated improved renal function in HRS (144–148). A mortality benefit was only demonstrated in responders to therapy (145). Terlipressin is not available in the US. In a retrospective study performed in the US, patients treated with

vasopressin had significantly higher recovery rates and improved survival when compared to octreotide alone (149). Furthermore, findings from three small observational and retrospective studies demonstrate improved outcomes with midodrine and octreotide (HRS reversal and decreased mortality) (150–152). These findings justify a larger RCT to appropriately evaluate this treatment modality.

Management of AKI in the ICU revolves around optimizing hemodynamics and renal perfusion, correcting metabolic derangements, providing adequate nutrition, and mitigating progression of injury. These management considerations are discussed.

Maintain Renal Perfusion. Optimization of renal perfusion may require volume resuscitation, inotropic, or vasopressor support. Extrapolated primarily from animal studies (62, 63), the human kidney has a compromised ability to autoregulate (maintain constancy of renal blood flow and GFR over a wide range of renal perfusion pressures) in AKI. Therefore, as a priority, prevention or management of AKI should include maintenance of hemodynamic stability and avoidance of volume depletion. A mean arterial pressure of ≥65 mm Hg is a generally accepted target; however, the data are limited (64, 65) and do not include patients with established AKI (loss of autoregulation). The level at which renal blood flow becomes dependent on systemic arterial pressure varies significantly based on age, underlying illness (e.g., hypertension), and the acute illness or condition (AKI, sepsis, and cardiopulmonary bypass). After volume resuscitation, blood flow should be restored to within autoregulatory parameters. This frequently requires vasopressor or inotropic support in the setting of septic shock, the most common cause of AKI in the ICU. There are currently no RCT comparing vasopressor agents; therefore, there is no evidence that, from a renal protection standpoint, there is a vasopressor agent of choice to improve kidney outcomes.

Decreased renal blood flow (attributable to either hypotension or high renal vascular resistance, from an imbalance between renal vasoconstriction and vasodilation) is a common feature in many forms of AKI. Consequently, there has been considerable interest in renal vasodilators to maintain renal perfusion for prevention or treatment of AKI. Whereas dopamine infusion may cause a transient improvement in urine output (66), "renal" dose dopamine does not reduce the incidence of AKI, the need for RRT, or improve outcomes in AKI (66–71). Furthermore, "low-dose" dopamine may worsen renal perfusion in critically ill adults with AKI (72) and is associated with increased myocardial oxygen demand and an increased incidence of atrial fibrillation (73). There is additional concern for extrarenal adverse effects of dopamine, including negative immunomodulating effects (74). Thus, there is broad consensus that dopamine is potentially harmful and without evidence of clinical benefit for either prevention or treatment of AKI. Therefore, its continued use for putative "renal protection" should be avoided.

Fenoldopam is a selective dopamine-1 receptor agonist approved for the treatment of hypertensive crisis (75). Paradoxically, the lowest doses of fenoldopam (≤1 μg/kg per min) are purported to increase renal blood flow without systemic effects. Despite encouraging data from pilot studies, (76–78) a prospective placebo-controlled study of low-dose fenoldopam in sepsis failed to decrease mortality or need for RRT despite a smaller increase in SCr (79). Larger studies to validate the meta-analytic observation that fenoldopam both reduces the need for RRT (OR, 0.54; $p = .007$) and decreases mortality (OR, 0.64; $p = .01$) (80) are currently ongoing in cardiac surgery patients (clinicaltrials.gov ID: NCT00557219).

Fluid Choice in AKI. The primary physiologic intention of volume resuscitation is the restoration of circulating volume to prevent or mitigate organ injury. The kidneys normally receive up to 25% of the cardiac output and are exquisitely sensitive to hypoperfusion attributable to true or relative hypovolemia. For this reason, the question of whether a particular type of fluid influences development of AKI is of pivotal importance.

Whereas crystalloid solutions remain the preferred treatment in usual care, the debate over whether colloid solutions provide any additional benefit remains an area of active investigation (81–85). In a landmark trial evaluating the impact of fluid choice on clinical outcomes, the SAFE study investigators randomized nearly 7000 patients to volume resuscitation with saline or albumin. They demonstrated no difference in survival or need for RRT between the two groups (86). In *post hoc* subgroup analysis, resuscitation with albumin was associated with increased mortality in critically ill patients after traumatic brain injury (87). In contrast, there was a trend toward improved survival in septic shock patients receiving albumin (30.7% in albumin group vs. 35.3% in saline group; $p = .09$) (86). Based on currently available literature, there is no evidence of a mortality benefit supporting the preferential use of albumin over crystalloids in a heterogenous critically ill patient population (84).

Synthetic colloids (e.g., hydroxyethyl starches, dextrans) are still widely used despite multiple reported safety concerns with regard to renal outcomes (88–90). An increased risk of AKI with the use of hydroxyethyl starches has been demonstrated in multiple small studies, and most recently a systematic review of 12 randomized trials demonstrated an increased risk of AKI with the use of hydroxyethyl starches among patients with sepsis (91). In contrast, the largest individual retrospective analysis (SOAP study cohort, 92) explored the effects of hydroxyethyl starches on renal function and did not find the use of hydroxyethyl starches to be an independent risk factor for AKI or need for RRT (93). The dose and preparation varied between studies. The adverse event profile has been linked, in part, to the individual preparation, with the lowest molecular weight offering the best side effect profile.

The question of fluid management does not end with the choice of fluid; careful consideration of the amount of fluid administered is also important. Critical illness is a dynamic process requiring frequent assessment of and adjustment to fluid status. In a prospective RCT of patients with acute respiratory distress syndrome, a fluid conservative strategy decreased ventilator days and did not increase the need for RRT (53). Furthermore, an observational study of >3000 patients demonstrated an association between positive fluid balance and increased mortality in patients with AKI (52). However, the question remains whether this is simply a marker of severity of illness or true causation; this observation warrants further investigation.

Avoid Hyperglycemia. Although the beneficial effects of intensive insulin therapy on mortality in critically ill patients remains controversial (94–96), two large RCT demonstrated a decreased incidence of AKI and a decreased requirement for RRT with tight glucose control (95, 96). Furthermore, a more detailed

secondary analysis strongly suggests that tight blood glucose control may be renoprotective in critically ill patients (97). Two smaller retrospective studies reported similar results (decreased incidence of AKI and decreased need for postoperative dialysis) in nondiabetic cardiac surgical patients (98) and in patients receiving total parenteral nutrition (99). However, in contrast, in the largest and most recent prospective RCT of intensive vs. conventional glucose control in >6000 critically ill patients, there was no difference in the number of patients requiring RRT (94). The overall incidence of AKI, however, was not reported in this study. It therefore remains unclear if there is a reno-protective role for tight glycemic control and, if present, whether any such effect is attributable to the avoidance of glucose toxicity or a beneficial effect of insulin. These findings warrant further study, especially in view of the fact that intensive glycemic control may be associated with a higher frequency of clinically relevant hypoglycemia.

Avoid Nephrotoxins. Nephrotoxic medications are a contributing factor in up to 25% of all severe AKI in critically ill patients (8, 9; Table 3*)*. Identification of at-risk patients is pivotal. Aminoglycosides, although less commonly used for severe Gram-negative infections than previously, are associated with significant nephrotoxicity. Although once-daily dosing of aminoglycosides has been shown, in some studies, to decrease the incidence of AKI (100, 101), published meta-analyses support comparable efficacy and decreased cost but do not consistently demonstrate a significant reduction in nephrotoxicity (102–106). Extended interval dosing should not be used in patients with CKD. Standard amphotericin B has been associated with AKI in 25% to 30% of patients (107). The lipid formulation of amphotericin B is preferred because of reduced nephrotoxicity of 19% vs. 34% (108). Caspofungin, a newer antifungal agent, is associated with an even safer renal profile (109). The use of aprotinin, a serine protease inhibitor used to decrease blood loss during cardiac surgery, has been associated with increased risk of AKI and need for dialysis (110).

ICU patients frequently have fluctuating renal function and a variable volume of distribution. Standard estimates of renal function are poor in critically ill patients. Therefore, medications must be carefully dose adjusted because of varied pharmacokinetics in critically ill patients with and without underlying CKD.

Diuretics in AKI. Use of diuretics in the prevention or treatment of AKI has physiologic merit but its use is not supported by prospective clinical study. Diuretics can increase urine output but have not been found to have a consistent impact on mortality (153–157). Mehta et al (157) demonstrated that failure to respond to diuretics was associated with an increased risk of death and non-recovery of renal function. Subsequently, in a large, prospective, multinational study, Uchino et al (158) did not demonstrate an increased mortality, thus leaving unresolved the therapeutic role of diuretics in critically ill patients with renal dysfunction. Although oliguric AKI has been associated with worse outcomes than nonoliguric AKI (159), there is no evidence supporting efforts to convert nonoliguric AKI with diuretics. Diuretics have not been found to shorten the duration of AKI, reduce the need for RRT, or improve overall outcomes (160). Furthermore, a recently published RCT comparing the use of furosemide vs. placebo in the recovery phase of AKI requiring continuous renal replacement therapy (CRRT), furosemide was found to increase urine output and sodium excretion but did not improve renal recovery (161). In a multinational survey, nephrologists and intensivists reported clinical uncertainty about the use of diuretics in AKI, thus justifying the need for a definitive RCT (162).

Because diuretic use in AKI has not been shown to decrease mortality, there is no role for diuretics to convert oliguric AKI to nonoliguric AKI. However, regarding an increased appreciation for the potential detrimental downstream effects of volume overload, it may be reasonable to try diuretics for control of volume overload. The clinician should, however, be careful not to delay initiation of RRT for volume overload in the critically ill patient with AKI.

Nutritional Considerations. Malnutrition in hospitalized patients is associated with increased mortality (163). Assessment of the nutritional status of critically ill patients is limited by the unreliability of traditional markers of nutritional status in critical illness in general, and AKI in particular. Prealbumin is excreted mainly by the kidneys and hence may be falsely elevated in patients with AKI (164). Patients with AKI are hypercatabolic with a negative nitrogen balance (165), resulting from both increased protein catabolism and impaired protein synthesis.

The impact of CRRT on nutrition in the ICU is two-fold. Because protein catabolism is markedly increased in most patients requiring CRRT (165–167), the use of CRRT enhances the clinician's ability to provide adequate nutrition because of an improved ability to manage volume. Unfortunately, the recommended amount of protein in this population remains controversial and recommendations are based solely on expert opinion, because there are no data available from RCT. Although there are no studies demonstrating a benefit in outcomes (e.g., survival or dialysis-free days), consensus recommendations include nonprotein caloric intake of 20 to 30 kcal/kg body weight per day and a protein intake of 1.5 g/kg per day (168). However, several studies have demonstrated a less negative or even positive nitrogen balance in those patients receiving up to 2.5 g/kg per day while receiving CRRT without evidence of adverse effects (169–171). An increase in nonprotein calories in critically ill patients with AKI does not improve nitrogen balance (172).

RRT for AKI in the ICU

Despite decades of clinical trials investigating potential pharmacologic interventions in AKI, current treatment options are primarily limited to RRT. Practice patterns vary widely regarding timing of initiation of RRT, dose delivered, and choice of modality as evidenced by international surveys (173–176). There is no current consensus on the indications for RRT for AKI. With a greater appreciation for and understanding of the role of the kidney in distant organ injury (177), it may be more appropriate to consider renal replacement therapy as renal supportive therapy (178). For the purposes of this review, we review the most up-to-date evidence available addressing timing, dosing, and modality of RRT.

Timing of Renal Replacement. There is little prospective data regarding the appropriate timing of initiation of RRT and that which are available are inconclusive. The "absolute" indications for initiation of dialysis (severe hyperkalemia, clinically apparent signs of uremia, severe acidemia, and volume overload, including pulmonary edema complicated by hypoxia or cardiogenic shock) are broadly accepted usual care standards.

Table 4. Summary of randomized controlled trials of dosing strategies for renal replacement therapy for acute kidney injury in the intensive care unit

Author	N	Design	RRT Modality	RRT Doses P/D	Survival
Randomized controlled trials with mortalitydifference					
Ronco et al (187)	425	Single center	CVVH (post-filter dilution)	(P) 20 mL/kg/hr (P) 35 mL/kg/hr (P) 45 mL/kg/hr	15-day: 41% 57% 58%
Schiffl et al (37)	160	Single center	Intermittent HD: daily vs. alternate day	Daily HD Kt/V(P) 1.19/(D) 0.92 Alternate day HD Kt/V (P) 1.21/ (D) 0.94	28 day: 72% 54%
Saudan et al (188)	206	Single center	CVVH vs. CVVHDF (pre-filter dilution)	(D) Mean: 25 mL/kg/hr/87% of prescribed (D) Mean: 42 mL/kg/hr/83% of prescribed (includes mean 24 mL/kg/hr replacement and 18 mL/kg/hr dialysate	28-day: 39% 59%
Randomized controlled trials without mortality difference					
Bouman et al (184)	106	Two centers	CVVH (post-filter dilution): early high-volume vs. early low-volume vs. late low-volume	(D) Mean: 48 ml/kg/hr (early) (D) Mean: 20 ml/kg/hr (early) (D) Mean: 19 ml/kg/hr (late)	28-day: 74% 69% 75%
Tolwani et al (189)	200	Single center	CVVHDF (pre-filter dilution)	(P) 20 mL/kg/hr/(D) 17 mL/kg/hr (P) 35 mL/kg/hr/(D) 29 mL/kg/hr	ICU discharge or 30 day: 56% 49%
Palevsky et al (190)	1124	Multicenter	Intensive vs. less intensive RRT (CVVHDF or SLED or HD)	(P) 21 mL/kg/hr or SLED or HD 3×/wk (D) 22 mL/kg/hr or Kt/V 1.3 3×/wk (P) 36 mL/kg/hr or SLED or HD 6×/wk (D) 35 mL/kg/hr or Kt/V 1.3 6×/wk	60 day: 44% 49%

P, prescribed; D, delivered; CVVH, continuous veno-venous hemofiltration; HD, hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; SLED, slow low-efficiency dialysis.

"Prophylactic" dialysis was introduced in the 1960s (179), and the first prospective study was published in 1975 comparing a BUN trigger of 70 mg/dL vs. nearly 150 mg/dL (180). Survival was 64% in the "early intervention" group as compared to 20% in the non-intensive or standard intervention group ($p < .01$). Conventional teaching based on this and other studies (181, 182) has been to initiate RRT before a BUN exceeds 100 mg/dL. Unfortunately, not only is the "ideal" BUN not established but also BUN *per se* is an imperfect reference value because it is widely influenced by nonrenal factors.

More recently, a review of the data from the PICARD study demonstrated an increased risk of death associated with initiation of RRT with a BUN >76 mg/dL in comparison to <76 mg/dL (183). An important limitation of this study is that patients who were conservatively managed (did not receive RRT) are "invisible" in this analysis, thereby limiting the validity of the findings regarding impact on mortality. In the only randomized study of timing of CRRT initiation (n = 106), there was no effect on mortality (184). "Early" dialysis was initiated after 6 hrs of oliguria. Of the 36 patients included in the "late" arm of this study, six patients did not receive RRT, of whom four survived, a fact that likely influenced the results of this study. Results from a large prospective multi-centered observational study of >1200 patients were internally inconsistent and dependent on the definition of "early" or "late" initiation of RRT (185). In this study, "late" initiation of RRT was associated with worse outcomes (higher crude mortality, longer duration of RRT, increased hospital length of stay, and greater dialysis dependence) when "late" was defined relative to date of ICU admission. However, there was no difference in crude mortality if the timing was defined by serum urea. Finally, there was a lower crude mortality if timing of RRT initiation was defined by SCr at initiation (higher SCr associated with a lower mortality) (185). Unfortunately, the question of timing remains unanswered and controversial (185, 186). There is clearly a need for a large RCT, with a clear definition of "early," to help guide the clinician in determining the appropriate timing for initiation of RRT for AKI in the ICU.

Choosing a Renal Replacement Dose. Six prospective RCT have been published addressing the question of dose of RRT in critically ill adults (37, 184, 187–190; Table 4). Three of these studies suggest that a higher dose of dialysis translates into improved outcomes, specifically decreased mortality (37, 187, 188). Ronco et al (187) published the first RCT in 2000 addressing this question. These investigators compared 20, 35, and 45 mL/kg/hr dosing strategies. There was a high mortality in all groups but a statistically lower mortality in the two groups with higher dose of ultrafiltration (35 and 45 mL/kg/hr) without any difference in complication rates between groups (187). In 2002, Schiffl et al (37) found daily dialysis to be superior to alternate day dialysis in a prospective randomized study. There were significantly fewer hypotensive episodes in the daily dialysis group (5% vs. 25%). In an intention-to-treat analysis, mortality was 28% for daily dialysis and 46% for alternate-day dialysis ($p = .01$) (37). An important limitation of this study is that the delivered dose was significantly less than the prescribed dose; therefore, the daily dialysis group received only "adequate" therapy as judged by contemporary standards. It may be said, therefore, that it was a comparison between adequate and inadequate dialysis. In 2006, Saudan et al demonstrated that continuous veno-venous hemodiafiltration (CVVHDF); addition of dialysate (1–1.5 L/hr) to continuous veno-venous hemofiltration (1–2.5 L/hr); improved 28-

and 90-day survival compared with hemofiltration alone in 206 critically ill adults; 39% vs. 59%; $p = .03$ and 34% vs. 59%; $p = .0005$, respectively, suggesting that small solute clearance is important (188).

In contrast, three prospective RCT have demonstrated no difference in mortality (184, 189, 190; Table 4). Bouman et al (184), in 2002, showed no difference in 28-day mortality when comparing early high-volume hemofiltration, early low-volume hemofiltration vs. late low-volume hemofiltration with the median dose (mL/kg/hr) of 48, 20, and 19, respectively. More recently, Tolwani et al (189) compared two different doses, 20 mL/kg/hr and 35 mL/kg/hr, of pre-filter CVVHDF and found no difference in 30-day mortality (44% vs. 51%, $p = .32$). Of note, the delivered dose in these two groups were 17 mL/kg/hr and 29 mL/kg/hr, respectively (189). The largest and only multi-centered trial designed to address the question of dose of RRT in critically ill adults is the acute tubular necrosis study published in 2008 (190). This was a two-arm study comparing intensive to standard RRT. The intensive therapy group underwent daily dialysis, CVVHDF, or sustained low-efficiency dialysis (SLED) at a dose of 35 mL/kg/hr, whereas the standard therapy group had alternate day dialysis (three times per wk), CVVHDF, or SLED at 20 mL/kg/hr. Notably, patients were able to move from intermittent to continuous modalities based on hemodynamic stability but they stayed within their assigned intensive or standard treatment therapy groups. There was no difference in the primary outcome, death from any cause (190). The RENAL study, comparing CVVHDF 25 mL/kg/hr to 40 mL/kg/hr, has completed enrollment but results have not yet been published.

An important factor in considering the results of the currently available data are the difference between study populations, use of solely convective or combination convective and diffusive modalities, and the potential gap between prescribed and delivered doses. Findings from these negative trials should not be interpreted to mean that dose is not important. On the contrary, it is likely that dose is important and, above a minimal dose, further escalation may not provide additional benefit. Based on currently available data, it is our recommendation that to ensure an actual delivered dose of 20 mL/kg/hr for continuous modalities one must prescribe a higher dose (e.g., 25 mL/kg/hr) to account for filter clotting, time off the machine for interventions, or radiographic studies, etc. For intermittent RRT, one should target a Kt/V of 1.2 to 1.4 per treatment for alternate day (three times per wk) hemodialysis. Furthermore, in addition to an appropriate target dose, there must be close attention given to the actual delivered dose. In summary, one dose does not fit all; RRT dose must be weight-adjusted.

Choosing a Renal Replacement Modality. Continuous RRT modalities more closely approximate normal physiology with slow correction of metabolic derangements and removal of fluid. Therefore, CRRT is commonly thought to be better-tolerated in the critically ill and hemodynamically unstable patient. The question of superiority remains given the absence of clear evidence that these apparent physiologic advantages translate into a decrease in ICU or hospital mortality (191–196).

Since 2000 there have been seven prospective RCT designed to address the important clinical question regarding optimal RRT modality (192, 193, 195, 197–200); of these, only three were multicentered studies (193, 198, 200). Of note, many of these trials, although published after 2000, enrolled patients in the 1990s. In six of the trials, mortality was the primary outcome. There have been several meta-analyses and systematic reviews comparing outcomes of intermittent vs. continuous renal replacement modalities with conflicting results (191, 201–204). A recent meta-analysis (nine randomized trials) comparing intermittent to continuous renal replacement therapy (intermittent RRT vs. CRRT) in AKI demonstrated no difference in mortality or renal recovery (defined as independence from RRT) (202). Of note, mortality was the primary outcome in eight of the nine included trials. Mortality, however, may not be the only clinically significant outcome. Two studies have shown that CRRT is associated with better long-term kidney recovery when compared to intermittent RRT (205, 206). In contrast, four RCT that included renal recovery as a primary outcome showed no difference in need for chronic RRT (193, 195, 198, 200). In the absence of definitive data in support of a particular modality (191, 201), the choice of RRT modality is currently influenced by multiple factors, including individual site availability, expertise, resources, cost, and likely clinician bias.

Hybrid therapies include SLED and extended daily dialysis. These modalities utilize standard intermittent hemodialysis machines but provide a slower solute and fluid removal similar to CRRT technologies. Although there have been no prospective randomized trials evaluating outcomes, hybrid therapies have been shown to be safe and effective alternatives to treating AKI in critically ill patients (207, 208).

The question of optimal modality has not yet been definitively answered. It is important to note that although the data strongly suggest that there is no difference in outcome between intermittent and continuous modalities, several key patient populations have been excluded. Namely, hemodynamically unstable patients, brain-injured patients, and those with fulminant hepatic failure were excluded and are widely believed to require continuous modalities. Furthermore, a critical limitation of all of the studies is the absence of a standardized dose (both within and between modalities) (202). RRT, like other medical treatments, must be considered in terms of dose adequacy to appropriately draw conclusions regarding clinical outcomes. Large randomized trials may be necessary to identify other potential subsets of patients who might benefit from continuous modalities.

Anticoagulation is frequently required to prevent clotting in extracorporeal circuits. There are no large RCT available to guide the choice of anticoagulation: heparin (unfractionated or low-molecular-weight heparin) or citrate-based protocols. Bleeding complications remain the primary concern with anticoagulation. Three small RCT, however, have demonstrated both similar or prolonged filter life and less bleeding and transfusion with citrate protocols when compared to use of heparins (209–211). In a recent larger, randomized, non-blinded trial comparing citrate to nadroparin, circuit survival was similar in both groups, but the citrate group had a lower mortality rate (212). Currently available data support the use of citrate for anticoagulation; however, this requires local expertise.

In summary, whereas RRT remains the cornerstone of treatment of AKI in the ICU, many key questions remain controversial. This is a rapidly evolving field and requires early consultation for appropriate expertise in the management of RRT for the critically ill patient with AKI.

On the Horizon

The identification of novel candidate biomarkers of early AKI provides hope for the success of future clinical early intervention trials. Advances in treatment of AKI have been limited by the inability to diagnose AKI early. Previously failed interventions may portend different outcomes if implemented earlier in the course of AKI. Novel pharmacologic agents on the horizon include erythropoietic agents and natriuretic peptides. Novel interventions include the use of stem cell therapy, renal tubule assist device, and high-flux hemofiltration for sepsis.

Candidate Biomarkers. Biomarkers of AKI in the ICU have three primary potential roles: early detection of AKI, differential diagnosis (e.g., hepatorenal syndrome vs. acute tubular necrosis), and prognosis (e.g., need for RRT or mortality). The ideal biomarker for AKI would be sensitive, specific, inexpensive, available noninvasively as a point-of-care test, and provide a real-time assessment of GFR. A panel of biomarkers or kidney function tests may be needed to address the complexity and heterogeneity of AKI in the ICU (213). Early identification of AKI with rapid and reproducible biomarkers is a critical first step toward improving outcomes in AKI.

According to several studies in critically ill patients, serum cystatin C is better than SCr for early detection of AKI (214, 215) and as a more sensitive marker of small changes in GFR (216–218). However, in one smaller study there was no correlation between cystatin C and SCr (219). In a recent study, urinary cystatin C but not plasma cystatin C was superior to conventional plasma markers in the early identification of AKI after cardiac surgery (220). Whereas rapid automated assays for cystatin C are currently available, more information on the use of cystatin C in the ICU setting and in specific patient populations (e.g., post-cardiothoracic surgery, sepsis, and trauma) is necessary before implementation in clinical practice.

Several studies support neutrophil gelatinase-associated lipocalin (221–227), kidney injury molecule-1 (228, 229), and interleukin (IL)-18 (222, 230, 231) as promising candidate biomarkers for the early detection of AKI. Point-of-care tests for urinary IL-18 and neutrophil gelatinase-associated lipocalin will likely be available for clinical use soon (213, 231–234). Urinary excretion of enzymes (alkaline phosphatase, gamma glutamyl transaminase, N-acetyl-beta-d-glucosamine) (235), transporters (sodium-hydrogen exchanger isoform 3) (236), cytokines (IL-6, IL-8, and IL-18), and protein-like substances (fetuin A) (237) are presumably "shed" into the urine with AKI; therefore, they may have a role in the early identification of AKI (232, 233).

In addition to emerging biomarkers, promising real-time imaging for use in early detection of AKI is on the horizon (238, 239). Ongoing discovery using urinary proteomic analyses or analysis of genetic polymorphisms may identify susceptibility to AKI (240–244). Overall, biomarkers in AKI, although rapidly evolving, are a field still in its relative infancy. Their role in the diagnosis and management of AKI in the ICU, although promising, remains unproven. Furthermore, judging novel biomarkers against an imperfect "gold-standard" biomarker (SCr) may have its limitations.

Erythropoietic Agents. The endothelium plays a central role in the initiation and maintenance phases of AKI. Animal models demonstrate a renal-protective effect of erythropoietin on endotoxin-related kidney injury (245). Decreased severity of AKI is proposed to occur through tubular regeneration from the direct effects of erythropoietin on tubular epithelial cells (246). These findings support the ongoing trials exploring the role of erythropoietic agents in the prevention or early intervention for AKI using early biomarkers (personal communication and clinicaltrials.gov NCT00476619).

Atrial Natriuretic Peptide. Recombinant human atrial natriuretic peptide decreased the need for dialysis (21% vs. 47%) and improved dialysis-free survival at 21 days (57% vs. 28%) in a RCT of 61 complicated post-cardiopulmonary bypass patients without preexisting CKD (247). Previously, however, in two multicentered, prospective, randomized trials in patients with acute tubular necrosis (248) or late oliguric AKI (249), atrial natriuretic peptide had no effect on need for dialysis or overall mortality. Further trials are needed before the use of atrial natriuretic peptide can be recommended for routine clinical use in cardiac surgery patients.

Renal Tubule Assist Device. Results from a recent RCT of the renal tubule assist device, in which the renal tubule assist device added to conventional CRRT was compared to CRRT alone, are promising with respect to both safety and efficacy. There was a non-statistically significant decrease in mortality at 28 days and a statistically significant difference at 180 days (secondary outcome) (250).

Hemofiltration for Sepsis. Payen et al (251) recently published the findings from the largest RCT of hemofiltration for severe sepsis and septic shock. At interim analysis, standard CVVH was found to be deleterious, with increased organ failures in the CVVH group compared to standard therapy. The study was stopped at interim analysis and consequently enrollment was insufficient to detect a difference in mortality with sufficient power. These findings contrast with those of Honore et al (252) in 2000, suggesting a beneficial role for hemofiltration in refractory septic shock. An important difference between these two studies was the delivered dose. In the first study, the dose, on average, was approximately 2 L/hr, whereas in the second study the dose was, on average, 8.7 L/hr for 4 hrs.

Stem Cells and the Kidney. Progenitor cell therapies represent an exciting future opportunity for treatment of AKI in the critically ill. Phase 1 trials of mesenchymal stem cells for treatment of patients at high risk for cardiac surgery-associated AKI are underway. A phase 2 RCT will be conducted if safety is demonstrated in phase 1 (clinicaltrials.gov ID: NCT00733876).

CONCLUSIONS

Many unanswered questions remain with respect to early identification, prevention, optimal timing, dose, and modality of RRT for AKI in the ICU. With respect to AKI in the ICU, the fundamental principal that guides all medical therapy—do no harm—is especially pertinent. AKI in the ICU most commonly results from multiple insults. Therefore, appropriate and early identification of patients at risk for AKI provides an opportunity to prevent subsequent renal insults and ultimately impact overall ICU morbidity and mortality. Strategies to prevent AKI in these patients are of pivotal importance. Key components of optimal prevention and management of the critically ill patient with AKI include maintenance of renal perfusion and avoidance of nephrotoxins. Whereas management of AKI remains limited primarily to supportive care, there are many potential therapies and interventions on the horizon.

Although it is widely accepted that early intervention therapies have been limited by the lack of tools for early detection, there are several promising candidate biomarkers in the pipeline. Furthermore, through the establishment of AKIN, an international and interdisciplinary collaborative network with the overarching objective to address AKI in the ICU, there has been tremendous progress in establishing a uniform definition (AKIN criteria) that is valuable for classification, clinical research study design, and prognosis.

A greater appreciation for the role of AKI in the ICU as an active contributor to morbidity and mortality is essential to furthering our knowledge and understanding of the influence of AKI in the critically ill patient. Early detection will facilitate early intervention. Early intervention designed to target the deleterious systemic effects of AKI will likely improve overall morbidity and mortality. For now, recognition of risk factors, excellent supportive care, and avoidance of clinical conditions known to cause or worsen AKI remain the cornerstone of management of AKI in the ICU.

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