

Renal Management in the Critically Ill Patient

Kenneth S. Waxman, MD*, Galen Holmes, MD

KEYWORDS

• Renal function • Acute kidney injury • Prerenal azotemia • Peritoneal dialysis

KEY POINTS

- Alterations in renal function are common in surgical patients, where multiple factors affect the clinical picture and outcomes are influenced by prompt diagnosis and protective management strategies.
- Recent studies suggest that acute kidney injury occurs in up to two-thirds of intensive care unit patients and that increasing severity of acute kidney injury is associated with increasing mortality.
- Urinalysis with microscopy is a useful tool in determining the cause of acute kidney injury.
- Distinguishing between prerenal azotemia and acute tubular necrosis, two of the most common causes of acute kidney injury, can be complicated by a confusing clinical picture.

INTRODUCTION

Alterations in renal function are common in surgical patients, where multiple factors affect the clinical picture and outcomes are influenced by prompt diagnosis and protective management strategies. This is particularly true in critically ill patients.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is defined by a decline in renal filtration marked by acute decrease in glomerular filtration rate (GFR). Although serum creatinine (S_{Cr}) is not a perfect marker for GFR, it is frequently used as a surrogate to estimate GFR. The true incidence of AKI and acute renal failure has been difficult to define, given the broad and various definitions used to quantify and study altered renal function. Recent introduction of consensus definitions, such as RIFLE criteria and Acute Kidney Injury Network (AKIN) staging, has allowed a more clear analysis of the impact of this problem. Recent studies suggest that AKI occurs in up to two-thirds of intensive care unit (ICU) patients and that increasing severity of AKI is associated with

Ventura County Health Care Agency, 2323 Knoll Drive, Ventura, CA 93003, USA

* Corresponding author.

E-mail address: kenneth.waxman@ventura.org

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increasing mortality.¹ It is clear that AKI is associated with increased morbidity, such as increased hospital length of stay and cost of care,² and has been linked to other in-hospital complications, such as increased difficulty weaning from mechanical ventilation.³ Preoperative risk factors for development of AKI include older age, emergent surgery, hepatic disease, obesity, high-risk surgery, and vascular disease in chronic obstructive pulmonary disease.⁴ Although the incidence of AKI seems to be rising, overall outcomes are gradually improving.^{5,6}

DEFINITION

The RIFLE criteria (Table 1), defined in 2004 by the Acute Dialysis Quality Initiative Group,⁷ quantifies the severity of AKI. Studies by Hoste and colleagues⁸ and Osterman and Chang⁹ found that mortality progressively increased with increasing RIFLE severity, and that patients in all of the RIFLE classifications had higher mortality than those in the ICU without AKI.

In 2005, the AKIN formulated consensus diagnostic criteria for AKI. The consensus states “an abrupt (within 48 hours) reduction in kidney function is currently defined as an absolute increase in S_{Cr} of either ≥0.3 mg/dL or a percentage increase of ≥50% (1.5-fold from baseline) or a reduction in urine output (documented oliguria of <0.5 mL/kg/hr for >6 hrs).” These criteria can only be applied in the face of adequate fluid hydration.¹⁰ This AKIN staging system (Table 2), arguably more inclusive than the RIFLE criteria, simplifies the definition of AKI for researchers and AKIN correlates with outcomes. Chertow and colleagues² found that an acute absolute change in creatinine greater than or equal to 0.3 was associated with increased mortality, length of stay, and cost of care. Barrantes and colleagues¹¹ found that patients meeting this definition of AKI were three times as likely to die during hospitalization.

In 2007, Coca and colleagues¹² published a review and meta-analysis of eight studies that suggest that even smaller elevations in S_{Cr} than recommended in RIFLE and AKIN (on the order of 10%–24%) are associated with a twofold risk of short-term death in several clinical settings and hypothesize that the lack of successful interventions in the treatment of AKI may be in part caused by delay in diagnosis caused by the lag-time of S_{Cr}. They suggest that implementing a new, more sensitive definition of AKI may improve the success of proposed interventions.

Table 1 RIFLE criteria		
	Serum Creatinine Criteria	Urine Output Criteria
Risk	Increased 1.5–2× baseline	<0.5 mL/kg/h for 6 h
Injury	Increased 2–3× baseline	<0.5 mL/kg/h for 12 h
Failure	Increased >3× baseline or Serum creatine >4 mg/dL with acute rise ≥0.5 mg/dL	<0.3 mL/kg/h for 24 h or Anuria for 12 h
Loss	Persistent renal failure for >4 wk	
End-stage renal disease	Persistent renal failure for >3 mo	

Data from Bellomo R, Ronco C, Kellum J, et al. Acute renal failure: definitions, outcome measures, animal models, fluid therapy and information technology needs. The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADOQI) Group. Crit Care 2004;8:R204–12.

Table 2
Acute Kidney Injury Network staging system

Stage	Serum Creatinine Criteria	Urine Output Criteria
I	Absolute increase ≥ 0.3 mg/dL or Increased $1.5\text{--}2\times$ baseline	<0.5 mL/kg/h for 6 h
II	Increased $2\text{--}3\times$ baseline	<0.5 mL/kg/h for 12 h
III	Increased $>3\times$ baseline or Serum creatine ≥ 4 mg/dL with absolute increase ≥ 0.5 mg/dL or Need for renal replacement therapy	<0.3 mL/kg/h for 24 h or Anuria for 12 h

Data from Mehta R, Kellum J, Shah S, et al. Acute Kidney Injury Network (AKIN): report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.

DIAGNOSTIC APPROACH

Historical keys include the temporal nature of symptoms, comorbidities, and identification of potentially nephrotoxic medications. It is important to identify signs and symptoms suggestive of obstruction. Although the physical examination in the intensive care patient with AKI is frequently fraught with conflicting clinical findings and is of limited accuracy,¹³ ascertaining clues to the patient's hemodynamics and volume status is valuable.

Urinalysis with microscopy is a useful tool in determining the cause of AKI. Presence of casts or other cells can suggest or confirm a diagnosis. Red cell casts suggest glomerulonephritis or vasculitis, whereas white cell casts may raise the possibility of interstitial nephritis or pyelonephritis. "Muddy brown" casts and renal tubular epithelial cells are pathognomonic for acute tubular necrosis (ATN) and differentiate ATN from prerenal azotemia, which has normal sediment or occasional hyaline casts.¹⁴ Dark heme-positive urine without red blood cells on microscopy is diagnostic of rhabdomyolysis.

Distinguishing between prerenal azotemia and ATN, two of the most common causes of AKI, can be complicated by a confusing clinical picture. Aside from analysis of urine sediment, response to fluid repletion is frequently used in this distinction. Return to baseline of renal function in 24 to 72 hours after fluid repletion suggests a prerenal cause. Urine chemistries can also aid in the diagnosis. The fractional excretion of sodium (FENa) measures the ratio of the sodium excreted to the sodium filtered by the formula:

$$\text{FENa} = (\text{urine sodium} \times S_{Cr}) / (\text{serum sodium} \times \text{urine creatinine}) \times 100$$

Prerenal azotemia is indicated by FENa less than 1%, whereas FENa greater than 1% suggests ATN. However, FENa may be spuriously low in patients with severe sepsis, heart failure, or cirrhosis despite the presence of ATN.¹⁵ The FENa may be falsely elevated in patients on diuretics, with glucosuria, or with preexisting renal insufficiency. In the case of diuretic use, the fractional excretion of urea (FEurea) can accurately distinguish between prerenal azotemia and ATN by the following formula:

$$\text{FEurea} = (\text{urine urea nitrogen} \times S_{Cr}) / (\text{blood-urea-nitrogen} \times \text{urine creatinine}) \times 100$$

Prerenal azotemia is indicated by a FEurea less than 35% and ATN by a value greater than 50%.¹⁶ Although of variable utility, other serum and urinary measures

can be used in aggregate to distinguish ATN from prerenal azotemia.^{17–20} These tests are summarized in **Table 3**, in order of general usefulness.

Serologic tests, such as antinuclear antibody, hepatitis B surface antigen, and anti-glomerular basement membrane antibody, are useful for distinguishing the cause of glomerular diseases. Creatinine phosphokinase level can indicate rhabdomyolysis.

Blood-urea-nitrogen (BUN) levels reflect the balance between urea production, metabolism, and excretion and frequently rise as renal function declines. Numerous nonrenal sources of BUN exist, including dietary protein intake, parenteral hyperalimentation therapy, catabolism of endogenous proteins, corticosteroid administration, and upper gastrointestinal bleeding. However, a recent study by Beier and colleagues²¹ suggests that elevation of BUN is predictive of long-term mortality, independent of normal creatinine.

BIOMARKERS

Most clinicians rely on changes in S_{Cr} and BUN as indicators of renal function because they are accessible and well established. However, S_{Cr} level is influenced by nonrenal factors, such as age, gender, race, body weight, muscle mass, protein intake, and drugs, and changes in this laboratory value tend to lag behind actual alterations in GFR. BUN is influenced by nutritional intake and the degree of catabolism, independently of renal function. For these reasons, alternatives to S_{Cr} and BUN serve as more specific markers, earlier indicators, and better prognostic tools for kidney injury. Belcher and colleagues²² highlight one of the most promising of these markers, interleukin (IL)-18. A proinflammatory cytokine thought to be released by injured proximal renal tubules,²³ IL-18 is a mediator and biomarker of AKI and can be reliably measured in the urine. The authors cite research that identifies IL-18 as an early indicator of AKI, as a tool for distinguishing prerenal azotemia and hepatorenal syndrome from ATN, and as a prognostic tool to predict mortality and viability of renal transplant.²² Belcher and colleagues²² also discuss neutrophil gelatinase-associated lipocalin, an acute-phase reactant indicative of inflammatory injury, which is upregulated and released by proximal renal tubular cells within a few hours of tubular damage. Like IL-18, studies suggest that neutrophil gelatinase-associated lipocalin can be used as an early indicator,²⁴ in the differential diagnosis, and as a prognostic tool for AKI.²⁵ Kidney injury molecule 1 is a type 1 cell membrane glycoprotein only expressed by proximal tubular cells in response to injury. It is detectable in urine and has been shown to discriminate ATN from other causes of AKI and is also used as a prognostic tool, because it predicts outcomes.²²

Table 3 Diagnostic indices distinguishing prerenal azotemia from acute tubular necrosis		
Measurement	Prerenal Azotemia	Acute Tubular Necrosis
Urinalysis	Normal or hyaline casts	Muddy brown casts
Response to fluid repletion	Within 24–72 h	No response
FENa	<1%	>1%
FEurea	<35%	>50%
BUN/creatinine ratio	20	10
Urine sodium (mEq/L)	<20	>30
Urine osmolality (mOsm/L)	>350	300

Abbreviations: BUN, blood-urea-nitrogen; FENa, fractional excretion of sodium; FEurea, fractional excretion of urea.

Cystatin C is a cysteine protease inhibitor secreted by all nucleated cells and is freely filtered by the glomerulus. Although several studies suggest that serum cystatin C is better than S_{Cr} as a surrogate for GFR and thus better for the early detection of AKI,^{26–29} another study suggests urinary cystatin C may be better.³⁰

Liver-type fatty acid binding protein is an intracellular lipid chaperone found in the proximal renal tubules where it binds lipid peroxidation products thus mitigating tissue damage in ischemia-reperfusion injury. Although urinary levels may be affected by liver injury or systemic inflammation, they are largely determined by tubular injury.³¹

IMAGING

Imaging is an important part of the initial work-up in patients with AKI. The primary test of choice is ultrasound. Using ultrasound to determine kidney size and echogenicity, cortical thickness, and the presence or absence of hydronephrosis is convenient and noninvasive.³² The presence of a thin rim of decreased echogenicity (“renal sweat”) may surround the kidneys in patients with kidney injury.³³ Recent studies suggest that the use of color Doppler technology is useful in the diagnosis of AKI.³⁴ Measuring the resistivity index, an indicator of perfusion based on measurement of flow at the level of the arcuate or interlobar arteries, may help differentiate among prerenal azotemia (normal resistivity index), ATN (reduced resistivity index), and postrenal obstruction (elevated resistivity index). The authors also suggest that this value can be serially followed, because it normalizes with resolution of the renal insult. Another promising ultrasonographic technique for the diagnosis of AKI is contrast-enhanced ultrasound, which makes use of microbubble-based contrast agents to help quantify renal blood flow, which is thought to be decreased in AKI.³⁵ Ultrasound is critical for the diagnosis of hydronephrosis in which it is more than 95% accurate in detecting dilation of the collecting systems and renal pelvis.^{36,37} A postrenal obstructive cause of AKI is suggested when hydronephrosis is present bilaterally.³⁸ Assessing bladder volume with ultrasound is important in the case of bilateral hydronephrosis. A postvoid residual volume greater than 150 mL is suggestive of bladder-outlet obstruction³⁹ and if observed in the presence of a urinary catheter, catheter malfunction should be considered. If ultrasound is negative, computed tomography (CT) may be required to elucidate the cause of obstruction, such as obstructing stones or pelvic mass.

MEDICATION REVIEW

When evaluating cases of AKI, a thorough investigation of medications and ingestions is essential. Certain medications can elevate S_{Cr} levels without affecting GFR, leading to misdiagnosis of AKI. The drugs cimetidine and trimethoprim block tubular creatinine secretion,^{40,41} whereas several drugs and substances interfere with the creatinine assay (**Table 4**). The drug tenofovir disoproxil fumarate, used in the treatment of HIV/AIDS, elevates S_{Cr} without affecting measured GFR by an undefined mechanism.⁴²

Various medications and substances induce AKI by several mechanisms (**Table 5**). It is important to limit the use of nephrotoxic agents when possible, especially in combination. If AKI is present, medications should be appropriately dosed.

DIFFERENTIAL DIAGNOSIS

Prerenal Azotemia

Prerenal azotemia is one of the most common etiologies of AKI, caused by a decrease in renal perfusion. This can occur because of an absolute decrease in extracellular

Table 4 Nonrenal causes of elevated serum creatinine		
Interference with Creatinine		
Assay	Block Tubular Creatinine Secretion	Undefined
Acetone (found in DKA)	Cimetidine	Tenofovir
Cefoxitin	Trimethoprim	
Flucytosine		
Isopropol alcohol		
Methanol		
Methyldopa		

Abbreviation: DKA, diabetic ketoacidosis.
Data from refs.^{82–85}

fluid volume (ie, hemorrhage, gastrointestinal losses, burns); a decrease in the effective circulating volume (ie, heart failure, portal hypertension); or shifting volume out of the intravascular space (ie, third-spacing). Prerenal azotemia by definition is reversible if treated early with fluid resuscitation, improvement in underlying heart failure, or correction of the third-space defect. If untreated, poor perfusion leads to tissue ischemia and cell death, representing a progression to intrinsic renal disease. An important cause of prerenal azotemia is abdominal compartment syndrome. High intra-abdominal pressures (>20 mm Hg bladder pressure) result in the clinical triad of oliguria, dyspnea with high peak airway pressures hindering ventilation, and hypotension transiently responsive to fluid resuscitation. If detected early, medical management can be effective,⁴³ but as with all compartment syndromes, timely surgical decompression with a decompressive laparotomy is usually necessary.

Postrenal Azotemia

Postrenal azotemia occurs because of obstruction of urinary flow at any point in the urinary tract from the renal collecting system to the level of the urethra. Increased back-flow builds pressure and decreases filtration. This type of azotemia can be caused by prostatic disease; neurogenic bladder; obstruction of an in-dwelling urinary catheter; abdominal or pelvic tumors; adhesions from prior surgery or radiation; vesicoureteral reflux; ureteral or bladder stones; medications causing crystals or fibrosis; or myeloma light chains (in multiple myeloma). The obstruction must be corrected to resolve the azotemia. Complications of postrenal azotemia include urinary tract infection secondary to urinary stasis, hyperkalemia caused by impaired excretion, and rarely postobstructive diuresis marked by significant diuresis leading to hypotension.

Intrinsic Renal Disease

Intrinsic renal disease results from injury to the parenchyma of the kidney, including the glomeruli, the interstitium, and the renal tubules.

Glomeruli

Glomerular disease is classified as nephritic or nephrotic and can have an acute or insidious onset. Nephritic syndrome is characterized by hematuria, proteinuria, hypertension, and edema caused by pores in the glomeruli allowing leakage of red blood cells and protein into the urine. Etiologies include bacterial endocarditis, systemic lupus erythematosus, poststreptococcal glomerulonephritis, hepatitis B antigenemia, IgA nephropathy, and hepatorenal syndrome. The hallmark of nephrotic syndrome is marked proteinuria with minimal hematuria and anasarca. Frequently, the diagnosis of

Table 5
Medications associated with direct and indirect nephrotoxicity

Direct Nephrotoxicity				Indirect Nephrotoxicity		
ATN	Osmotic Nephrosis	Interstitial Nephritis	Glomerular Injury	Decrease in Intrarenal Blood Flow		Volume Depletion
Iodinated contrast	Hypertonic solutions	NSAIDs	NSAIDs	Crystal deposition (intrarenal obstruction)	Retroperitoneal fibrosis (ureteral obstruction)	Diuretics (loop, mannitol, thiazide)
Aminoglycosides	IVIG	Beta-lactams	Zoledronate	Indinavir	Ergotamine	
Amphotericin B		Quinolones	Pamidronate	Sulfadiazine	Sotalol	
Petamidine		Sulfonamides	Ticlopidine	Sulfamethoxazole	Propranolol	
Foscarnet		Phenytoin	Clopidogrel	Methotrexate	Bromocriptine	
Cisplatin		Allopurinol	Cyclosporine	High-dose acyclovir		
Acetaminophen		Thiazide and loop diuretics	Gemcitabine			
Cidofovir		Indinavir				
Adefovir		PPIs				
Tenofovir		Vancomycin				
Melphalan						
IVIG						
Hetastarch						
Mannitol						

Abbreviations: ATN, acute tubular necrosis; IVIG, intravenous immunoglobulin; NSAIDs, nonsteroidal inflammatory drugs; PPIs, proton pump inhibitors.

Data from Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. *Crit Care Med* 2008;36(4):S216–23.

nephrotic syndrome requires renal biopsy. Causes include minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy.

Interstitial

There are many conditions affecting the renal interstitium including allergic; drug-induced; infectious (bacterial, viral, fungal, parasitic); autoimmune (systemic lupus erythematosus, Sjögren syndrome, Goodpasture syndrome); infiltrative (lymphoma, sarcoid); and idiopathic forms of disease. The most common cause of acute interstitial nephritis is drug-induced disease, which is thought to underlie 60% to 70% of cases.⁴⁴ Illicit drugs, penicillins, cephalosporins, sulfonamides, and nonsteroidal anti-inflammatory drugs are some of the most common offenders. Acute interstitial nephritis can cause fever, rash, eosinophilia, and eosinophiluria; however, none of these are reliably diagnostic. Kidney biopsy is the gold standard of diagnosis, but rarely needed. Timely discontinuation of the offending agent is usually effective treatment. The use of steroids in drug-induced acute interstitial nephritis is controversial, but a recent study suggests that early administration of steroids (within 2 weeks) may prevent long-term sequelae.⁴⁵ Hyperuricemia, hyperuricosuria, and hyperphosphatemia, seen in tumor lysis syndrome, can cause deposits of crystals in the renal interstitium and tubules, leading to AKI. Similarly, ingestion of oral sodium phosphate solutions in bowel preparations for colonoscopy has been recognized as a cause of AKI from crystal deposition.⁴⁶ Allupurinol and rasburicase have been used for the prevention and treatment of tumor lysis syndrome.⁴⁷

Tubules

ATN was originally thought to be caused by a period of ischemia followed by reperfusion causing extensive necrosis. More recently investigators emphasize the role of endothelial dysfunction, systemic inflammatory mediators, and oxidative stress in causing AKI.⁴⁸ With this in mind, the term currently is more often used to describe a clinical situation with adequate renal perfusion to maintain tubular integrity but not enough to sustain glomerular filtration.⁴⁹ This is particularly true in the case of sepsis and shock of any cause. ATN is also caused by toxins, most commonly the aminoglycoside antibiotics. Other toxins causing ATN include platinum, antifungals, rhabdomyolysis, hemolysis, and radiographic contrast (see [Table 5](#)). Risk factors for ATN include volume contraction, age, and concomitant use of other nephrotoxins. Prevention of ATN is focused on achieving euolemia while maintaining renal perfusion and avoiding further renal insults. Rhabdomyolysis is caused by massive breakdown of muscle, releasing myoglobin, which can result in ATN. Rhabdomyolysis can be precipitated by drugs (heroin, cocaine, statins, alcohol); multiple trauma; crush injuries; seizures; muscle compression; and extreme exertion. Contrast-induced nephropathy (CIN) is an acute decline in renal function seen after administration of intravenous radiographic contrast, specifically an increase in S_{Cr} of 25% above baseline or absolute increase of 0.5 mg/dL within 48 hours after administration of parenteral contrast. Although not well understood, it is likely the result of several factors. Transient hypotension caused by osmotic diuresis, vasoconstriction of glomerular vessels, and direct cytotoxic effect has been hypothesized.⁵⁰ CIN is the third most common cause of hospital-acquired renal injury and is most prevalent among those with underlying renal disease.⁵¹ Nephrogenic systemic fibrosis is a recently diagnosed disease that occurs in patients with preexisting stage IV and V chronic kidney disease or acute renal failure that has been linked to intravenous administration of gadolinium-based contrast media for magnetic resonance imaging. Shortly after exposure to gadolinium (2–12 weeks) patients develop skin thickening and fibrosis, similar to scleroderma, and

can have rapid progression to joint contractures and severe disability. Systemic involvement may occur, leading to cardiomyopathy, pulmonary fibrosis, pulmonary hypertension, diaphragmatic paralysis, and death. The pathophysiology of the disease still remains unclear, but recent studies have demonstrated gadolinium deposits in tissues of patients diagnosed with nephrogenic systemic fibrosis.⁵² Currently, prevention of nephrogenic systemic fibrosis entails avoidance of gadolinium administration in this population. Several treatment options (steroids, intravenous immunoglobulin, UV light, renal transplant) have been studied and have some benefit, but the evidence is based on small case studies or case reports and requires further evaluation.

RENAL PROTECTIVE STRATEGIES

Prevention of CIN

It is generally accepted that low-volume nonionic low-osmolar or iso-osmolar contrast media are associated with a decreased incidence of CIN than the high-osmolar agents.⁵³ For this reason, the high-osmolar preparations should be avoided. Such agents are currently not commonly used in clinical practice. Volume expansion has been accepted as the primary prevention of CIN, although choice of fluid has been controversial. Several meta-analyses of isotonic sodium bicarbonate show benefit over isotonic saline. However, a recent randomized controlled trial (RCT) suggested no difference between the two fluids, both of which were beneficial in preventing CIN.⁵⁴ Although the evidence suggests that bicarbonate may be superior, adequate volume resuscitation with either fluid is acceptable. *N*-acetylcysteine is a free radical scavenger that has been shown to decrease the incidence of CIN compared with placebo⁵⁵ and saline alone.⁵⁶ However, several studies found no benefit to *N*-acetylcysteine in the prevention of CIN. Despite an unproved benefit, because it is safe and inexpensive, many experts recommend *N*-acetylcysteine for its possible benefit.⁵⁷

Other Preventative Strategies

The most important priority in renal protection is to maintain renal perfusion. Fluid choice, specifically crystalloid or colloid, for this purpose has been controversial. The landmark SAFE study⁵⁸ compared saline and albumin and found no difference in survival or need for renal replacement therapy (RRT) between the two groups. However, in post hoc analysis, albumin was found to have increased mortality in traumatic brain injury and a trend to decreased mortality in septic shock.

The use of synthetic colloids for volume expansion has been cautioned because of numerous studies implicating an increased risk of renal dysfunction. This increased risk of AKI was confirmed by a recent systematic review of the use of hydroxyethyl starches in patients with sepsis⁵⁹ and suggests that its use should be avoided. When fluid resuscitation is administered in critically ill patients, the amount given is also an important decision. An observational study in patients with AKI reported increased mortality associated with a positive fluid balance⁶⁰ and an RCT in patients with acute lung injury reported fewer ventilator days with conservative fluid management, which did not increase the need for RRT.⁶¹ Erythropoietin has some promising nonerythropoietic properties, including tissue protection and antiapoptotic effect in animal models of brain, heart, and kidney. Despite preclinical data showing protective effects in AKI, the EARLYARF RCT in humans did not show benefit in erythropoietin administration.⁶² However, proponents of erythropoietin cite the use of poorly validated biomarkers, among other flaws in study design that may have been responsible for the apparent failure.⁶³ The use of diuretics, such as mannitol and furosemide, in the prevention and treatment of AKI is extensive but they have not been conclusively found

to shorten the duration of AKI, reduce the need for RRT, or improve overall outcomes.⁶⁴ Although it is based on anecdotal studies performed in the early 1960s, the prophylactic use of mannitol, together with an adequate hydration policy, is standard practice in many vascular and cardiac surgical units. Mannitol is beneficial in preventing ATN in postrenal transplant patients⁶⁵ and in severe crush injury.⁶⁶ In a recent study, high-dose furosemide showed a protective effect on mortality in patients with acute lung injury but no significant effect after adjustment for post-AKI fluid balance, which when positive, was strongly associated with mortality.⁶⁷ Atrial natriuretic peptide seems to dilate afferent glomerular arterioles and constrict efferent glomerular arterioles and may selectively increase GFR. It also inhibits agents that vasoconstrict the glomerular blood flow. Although the most recent RCT shows promising results in reducing the need for dialysis in cardiac surgery patients,⁶⁸ previous studies did not show any benefit.^{69,70} Further studies are needed before its use is recommended.

It has been shown that dopamine at low doses increases renal perfusion and GFR and for this reason, dopamine was evaluated for its role in renal protective strategies. Despite numerous studies on this subject, none have yielded evidence to support this use of dopamine, and some results suggest it may worsen renal perfusion.⁷¹ Fenoldopam, a dopamine-1 receptor agonist used in hypertensive emergencies, increases renal blood flow at its lowest dose. Although it failed to show benefit in sepsis, it has shown promise in surgical patients and the critically ill. In a recent meta-analysis of 16 randomized trials it seems to reduce mortality and need for RRT.⁷²

A promising study by Heemskerk and colleagues⁷³ reports a significant decrease in plasma creatinine after an infusion of alkaline phosphatase in intensive care patients with severe sepsis or septic shock. The authors propose that exogenous alkaline phosphatase attenuates production of nitric oxide, a systemic vasodilator that causes compensatory renal vasoconstriction, by inhibiting inducible nitric oxide synthase, an enzyme that catalyzes production of nitric oxide. Reduction in nitric oxide may protect renal function; however, larger trials are needed to determine the presence of morbidity or mortality benefit. Other agents evaluated for potential use in prevention of CIN or ATN include theophylline and prostaglandin E₁. Both have shown promising but conflicting results, requiring further study before their use is recommended.

TREATMENT

Nonrenal Care that Affects AKI

It is clear that hyperglycemia and hypoglycemia during the postoperative period or during critical illness correlate with adverse outcomes. A recent study in surgical ICU patients also suggests that the presence of hyperglycemia and hypoglycemia in the same patient is associated with higher mortality risk.⁷⁴ Several studies suggest that intensive insulin therapy is associated with decreased incidence of AKI and reduced need for RRT, and may be renoprotective in critically ill surgical patients.⁷⁵ However, the largest and most recent RCT comparing intensive insulin therapy with conventional glucose control found no difference in need for RRT.⁷⁶ Lung protective ventilation is a mainstay in the treatment of acute respiratory distress syndrome because of the ARDSnet trial, which also suggested that the low-volume ventilation also may be beneficial for the kidney. The damaging effects of high-volume and high-pressure ventilation have been increasingly reported⁷⁷ and validate the use of lower volumes.

Renal Replacement Therapy

Despite numerous clinical trials evaluating pharmacologic agents for use in treating AKI, RRT remains the mainstay in treatment. Approximately 4% of critically ill patients

who develop AKI require RRT.⁷⁸ The goal of RRT in AKI is to support nonrenal organs while awaiting recovery of renal function. However, standardization of practice in regards to initiation, dose, and modality of RRT has not been established and remains controversial.

Timing of initiation of RRT

Generally accepted indications for initiation of dialysis include severe acidemia, severe hyperkalemia, ingestion of a dialyzable substance causing renal injury, volume overload, and clinically apparent signs of uremia. Evidence suggests a benefit to early initiation; however, each study has variable definitions of early and late and differing markers to trigger initiation, including BUN, oliguria, ICU admission, and S_{Cr} .⁷⁹ Continued studies are needed to further define optimal initiation.

Frequency and rate of RRT

When determining the appropriate dose of dialysis, wide variation in clinical practice exists. Numerous studies are available, but there are conflicting data on outcomes. The largest and only multicenter trial looking at outcomes related to amount of renal support was the Acute Renal Failure Trial Network Study.⁸⁰ This study, following customary practice, assigned hemodynamically stable patients to the intermittent hemodialysis (IHD) group and hemodynamically unstable patients to continuous renal replacement modalities. The intensive management strategy had IHD six times per week or continuous therapy at 35 mL/kg/h. The less intense management strategy had IHD three times per week or continuous therapy at 20 mL/kg/h. They found no significant difference between groups in 60-day survival or renal recovery.

Modalities for RRT

Peritoneal dialysis is a simple but limited method for clearance of solute and ultrafiltration. It offers hemodynamic stability but can compromise respiratory status because of the dialysate volume. Its role in the ICU is therefore limited. Ultrafiltration is a technique that allows rapid removal of volume without significant solute removal. This protects intravascular volume and causes less hypotension. This strategy is useful in treating volume-overloaded states. IHD is the most frequently used method for RRT in the United States. This method uses a semipermeable biocompatible synthetic membrane and an electrochemical gradient maintained by continuous dialysate flow to remove solute. The major benefit of IHD is rapid removal of solute. Volume removal is frequently limited by hypotension. Another frequent drawback is hypoxia during treatments. Continuous renal replacement therapies are commonly used for RRT internationally, but used less frequently in the United States. Continuous therapies use hemofiltration, a technique that, like ultrafiltration, removes volume, but also has equal removal of solute because of the high permeability of the membrane used. In this case, solute clearance is dependent on volume filtered and because the volume filtered is substantial, replacement fluid is infused continuously to avoid hemodynamic instability. Hemodiafiltration adds a dialysate flow to supplement hemofiltration clearance. It is unclear if this addition adds benefit to hemofiltration alone. Continuous venovenous hemofiltration and continuous venovenous hemodiafiltration are two frequently used methods of CRRT that have been compared with IHD. It was initially thought that these continuous methods were safer for hemodynamically unstable patients and more physiologic and thus better for the critically ill. However, studies to determine the optimal method of RRT have yielded contradictory results. In a recent meta-analysis of nine randomized trials, Bagshaw and colleagues⁸¹ found no difference in mortality or renal recovery between continuous and intermittent modalities. They comment on numerous problems with study design and quality that may

undermine the results. Other drawbacks to the continuous modalities are the higher cost and need for anticoagulation. Hybrid therapies exist and have not yet been evaluated by prospective randomized trials. The most common hybrid modality is slow low-efficiency dialysis. Slow low-efficiency dialysis is a technique that is based on the observation that slower flow and longer treatments of IHD improve the inherent hemodynamic instability. Slow low-efficiency dialysis is usually continued over 8 to 12 hours nightly, avoiding typical daytime interruptions (procedures, radiology, surgery) and allowing for daytime mobilization. Presently, many questions regarding the variables of RRT remain unanswered and current practice is based largely on clinician choice, available resources, and cost.

SUMMARY

AKI is common in the hospital setting and morbidity and mortality outcomes depend on early recognition and early intervention. Identifying patients at risk of AKI is critical in prevention, early identification, and appropriate treatment.

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