JAOA REVIEW

Acute Kidney Injury: New Concepts in Definition, Diagnosis, Pathophysiology, and Treatment

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Acute kidney injury (AKI) is increasingly recognized in all fields of medical practice. Unfortunately, this syndrome has been plagued by inconsistent definitions, simplistic pathophysiologic schemas, and insensitive diagnostic tools. Recent advances in defining AKI, understanding its pathophysiology, and improving the diagnostic accuracy of the testing tools available eventually will impact disease management and clinical outcomes. Prompt recognition and treatment of AKI remain the cornerstone of clinical management for this high-mortality, high-cost syndrome. The authors provide the most recent updates in the definition, diagnosis, pathophysiology, and treatment options for patients with AKI, providing a stepwise approach to clinical evaluation for use in all fields of medical practice.

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Acute kidney injury (AKI) is commonly encountered in the hospital and outpatient settings and is associated with a high rate of mortality. Despite improvements to our understanding of its pathogenesis, many aspects of AKI remain subject to debate and incongruity.

Acute kidney injury has been documented in up to 7% of hospitalized patients on the basis of several single-center reports.[1,2] In addition to demonstrating a potent, independent effect on mortality,[3] AKI is associated with a significantly increased length of hospital stay and high financial costs across a broad spectrum of conditions.

In fact, Chertow et al[4] found an increase of serum creatinine levels greater than or equal to 2.0 mg/dL was associated with an almost $34,000 mean unadjusted increase in total hospital costs. In addition, a serum creatinine rise of 0.5 mg/dL or more correlated with a more than sixfold increase in the odds of death.[4] These findings highlight the importance of prompt diagnosis and treatment of this ubiquitous condition.

The present review describes the most current concepts regarding the definition, diagnosis, pathophysiology, and treatment of AKI.

Definition

A uniform and precise operational definition of AKI (formerly *acute renal failure [ARF]*) has remained somewhat elusive.[5] However, a recent proposal by the Acute Kidney Injury Network[6] appears to have gained clinical acceptance. In that initiative, the group[6] outlined two options for measuring the abrupt (≤48 hour) reduction of kidney function that signifies AKI:

- increased serum creatinine levels (absolute, ≥0.3mg/dL; percentage, ≥50%; or 1.5-fold from baseline), or
- oliguria (<0.5mL/kg/h for more than 6 hours)

The term AKI is intended to emphasize the reversible nature of most renal insults. The term *ARF* is now generally reserved to describe the condition of patients who sustain kidney injury that necessitates renal replacement therapy (RRT) (ie, any method of conventional or intermittent dialysis).

Medical understanding of AKI was augmented by the RIFLE criteria.[7-9] The acronym *RIFLE* defines AKI with three grades of increasing severity (Risk, Injury, Failure) and outlines two outcome variables (Loss and End-stage). This system, much like that of the Acute Kidney Injury Network,[6] describes the severity of renal dysfunction on the basis of increase in serum creatinine levels and decline in urine output (*Figure 1*).

The RIFLE criteria has been validated in clinical settings for predicting patient outcomes.[10] Hoste et al[11] observed that the three grades described in the RIFLE criteria—risk, injury, and failure—were associated with inpatient mortality rates of 8.8%, 11.4%, and 26.3%, respectively.

It is anticipated that these more precise and universal definitions of AKI will aid clinicians in rapid recognition of at-risk patients.

New Biomarkers

And yet, serum creatinine levels demonstrate poor sensitivity and specificity in this setting, slowing recognition and therapeutic management of AKI. However, several other biomarkers

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Class	Increase in Glomerular Filtration Rate	Reduced Urine Output by Symptom Duration
■ **Severity**		
□ Risk	1.5-fold	<0.5 mL/kg/h for 6 h
□ Injury	twofold	<0.5 mL/kg/h for 12 h
□ Failure	threefold*	<0.3 mL/kg/h for 24 h†
■ **Outcome**		
□ Loss—Persistent acute kidney injury with complete loss of function for more than 4 wk		
□ End-stage—End-stage kidney disease for more than 3 mo		

Figure 1. *The RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria for acute kidney injury,[7-9] which defines this syndrome based on glomerular filtration rate (ie, serum creatinine increase) and weight-dependent urine output criteria. *A threefold increase in serum creatinine or a serum creatinine level ⩾4.0mg/dL with an acute rise >0.5 mg/dL indicates renal failure. †Likewise, anuria for 12 hours indicates renal failure.*

have shown promise in assisting physicians detect decrements in renal function.

Cystatin C is a cysteine protease inhibitor that is released at a constant rate by all nucleated cells.[12] It is freely filtered by the glomerulus and is completely reabsorbed, not secreted, by the tubules.[12] Studies[13,14] have shown cystatin C to be at least as good as serum creatinine in estimating GFR in chronic kidney disease (CKD)—and probably a better estimator of GFR in AKI.

Neutrophil gelatinase–associated lipocalin,[15] kidney injury molecule-1[16], and interleukin 18[17] have likewise shown promise for representing the "troponin-like" molecule of AKI. If validated, these molecules will offer substantial advantages over serum creatinine in the early detection of AKI.

If renal injury can be diagnosed sooner in its etiologic process, therapeutic interventions can be instituted more promptly, thereby improving secondary disease prevention.

Pathophysiology

The mechanisms involved in the etiology of AKI are as follows:

□ endothelial injury from vascular perturbations
□ direct effect of nephrotoxins
□ abolishment of renal autoregulation
□ formation of inflammatory mediators (*Figure 2*)

Necrosis and apoptosis of tubular cells lead to tubular obstruction, which contributes to the reduction of GFR.[18] In addition, elevated intracellular calcium levels from tubular damage cause a series of cellular-level alterations that culminate in increased tubuloglomerular feedback, and thus, diminished GFR.[18]

Vascular compromise causes increased cytosolic calcium, elevated endothelial injury markers, and production of inflammatory mediators (eg, tumor necrosis factor α, interleukin 18, intercellular adhesion molecule 1), which result in reduced GFR.[18]

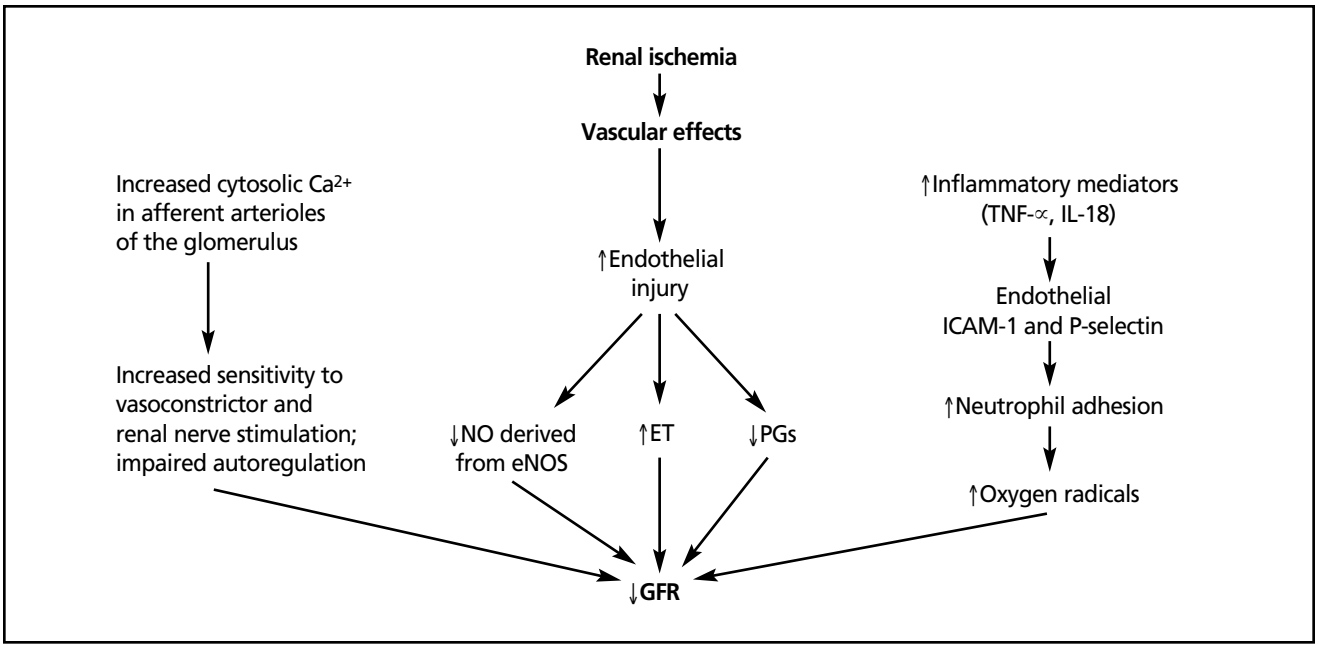

Figure 2. *Mechanisms of acute kidney injury: a molecular viewpoint. Cascade of events involved in the pathophysiology of acute kidney injury. (Copyright 2004 by American Society for Clinical Investigation. Reproduced with permission of American Society for Clinical Investigation.* J Clin Invest. *2004;114:8.[18])*

These pathophysiologic mechanisms are perpetuated by a persistent imbalance between the mediators of vasoconstriction and -dilatation that result in intrarenal vasoconstriction and, eventually, ischemia. The vasoconstrictors include angiotensin II, endothelin, thromboxane, and adenosine. The vasodilators include prostaglandin I2 and endothelial-derived nitric oxide.

High levels of vasoconstrictors and low levels of vasodilators cause continued hypoxia and cell damage or cell death. Endothelial-derived nitric oxide is under investigation as a potential therapeutic option to help break this cycle of ischemia.[19]

Continued research into the pathophysiology of AKI may yield potential targets in the clinical management of this syndrome.

Diagnostic Evaluation

Multiple serum and urinary laboratory values or indices can help physicians distinguish among prerenal, renal, and postrenal causes of AKI (*Figure 3*).

The fraction of filtered sodium (FeNa) that is excreted in the urine serves as a useful tool in assessing the tubular integrity of a functioning nephron, primarily in an oliguric state. A FeNa (urine sodium × plasma creatinine ÷ plasma sodium × urine creatinine) level of less than 1% has a diagnostic accuracy of approximately 80% for prerenal azotemia.[18] Other conditions associated with FeNa levels of less than 1% include sodium-avid states (eg, congestive heart failure, cirrhosis, nephrosis), contrast-induced nephropathy, rhabdomyolysis, and severe glomerulonephritis (glomerular nephritis).

In addition, a patient's FeNa level may be misleading (ie, inappropriately elevated) in the setting of CKD, diuretic use, and glycosuria. The calculated fractional excretion of urea (FeUrea) can function as a surrogate for FeNa when patients have received diuretic therapy.

An FeUrea level of less than 35% suggests prerenal etiology. A urine osmolality higher than 500 mOsm/L, a blood urea nitrogen to creatinine ratio greater than 20 to 1, urine sodium less than 20 mEq/L, and bland urine sediment all support a diagnosis of prerenal azotemia.

Indices	Prerenal	Renal
Blood urea nitrogen to creatinine ratio	>20	<20
Fraction of filtered sodium, %	<1	>2
Fractional excretion of urea, %	<35	>35
Urine osmolality, mOsm/L	>500	<400
Urine sediment, cast type	bland, hyaline	granular
Urine sodium, mEq/L	<20	>40

Figure 3. *General guidelines for differentiating the etiology of acute kidney injury (ie, prerenal vs renal) using laboratory studies.*

Conversely, a urine osmolality of less than 400 mOsm/L, high urine sodium (ie, >40 mEq/L), and urine sediment with muddy brown or granular casts suggests tubular injury.

Renal ultrasonography aids in ruling out postrenal etiology of AKI.

Causes

Once a diagnosis of AKI has been established, it is important to stratify the patient's condition by etiology (ie, prerenal, renal, or postrenal). Stratification is important because recommended therapeutic models are tailored to these categories.

Prerenal

Prerenal AKI is secondary to underperfusion of otherwise normal, functioning kidneys. The hallmark of prerenal AKI is rapid reversibility. Prerenal kidney injury can result from volume depletion that is the result of renal or extrarenal losses, fluid sequestration, or inadequate perfusion pressures secondary to heart failure, cirrhosis, or sepsis.

For patients with prerenal AKI, urinalysis is typically bland or with hyaline casts, urine sodium is low (ie, <1%), and urine osmolality is high.

Brisk correction of kidney injury with volume repletion supports a prerenal etiology. Conversely, kidney injury refractory to fluid administration suggests an intrinsic renal process.

Renal

The causes of intrinsic renal disease can be categorized by anatomy: tubular, interstitial, glomerular, and vascular. Microscopic analysis of the urine is integral to localizing the site of nephron damage.

Tubular damage usually results in muddy brown, granular casts. Interstitial damage can result in white blood cell cast formation. Microscopic analysis of glomerular—and to a lesser extent microvascular—damage reveals red blood cell (RBC) casts and dysmorphic RBCs.

■ **Tubule**—Acute tubular necrosis (ATN) results from prolonged exposure to a prerenal milieu (ie, ischemic) or from direct toxin damage (ie, nephrotoxic). The list of nephrotoxic agents is broad and ever-expanding (*Figure 4*).

The classic course of "self-limited" ATN is a steady rise in serum creatinine levels (injury stage), followed by stabilization (plateau stage), and an eventual decline in those measures (recovery stage) during 7 to 21 days. This pattern correlates with the injury and death of tubular cells, their regeneration, and, eventually, recovery of renal tubule function.

It should be noted, however, that fluctuations in serum creatinine levels are dependent on many variables (eg, severity and duration of initial renal insult, time to improve the injurious environment, degree of underlying kidney reserve) and therefore cannot be expected in all cases of ATN.

Microscopic evidence of granular casts and supportive urinary indices—all within the appropriate clinical setting—

Acyclovir
Aminoglycosides
Amphotericin B
Benzoylmethyl ecgonine (cocaine)
Cisplatin
Cyclosporine
Foscarnet sodium
Highly active antiretroviral therapy
Intravenous immunoglobulin therapy
Medical contrast media (eg, hyperosmolar radiocontrast media)
Nonsteroidal anti-inflammatory drugs
Penicillin
Tacrolimus

Figure 4. *Nephrotoxic agents.*

remain the best way to diagnose ATN. Imediate discontinuation of nephrotoxic agents and restoration of adequate hemodynamics are paramount in the prevention and management of ATN.

■ **Interstitium**—Acute interstitial nephritis (AIN) is classically heralded by depressed renal function in the setting of fever, rash, leukocytosis, and eosinophiluria. White blood cell casts are occasionally seen on urine microscopy. Acute interstitial nephritis is usually drug induced, though certain infections and neoplastic disorders have also been associated with this condition.

It should be emphasized that eosinophiluria is a nonspecific test for which positive results are achieved in about 50% of confirmed cases.

Other causes of eosinophiluria are prostatitis, rapidly progressive glomerulonephritis, and atheroembolic renal disease.

The primary therapeutic option for patients with AIN is to remove the offending agent, if possible. High-dose corticosteroids have variable success rates among patients with AIN.[20]

■ **Glomerulus**—Red blood cell casts, proteinuria, or both suggest the presence of glomerular disease. Hematuria, RBC casts, hypertension, and mild proteinuria suggest a nephritic process (ie, acute glomerulonephritis).

The differential diagnosis for glomerulonephritides includes primary, infectious, and rheumatologic or vasculitic conditions. A standard work-up for a patient with presumed glomerulonephritis includes (but is not limited to):

□ antineutrophilic cytoplasmic antibody
□ antinuclear antibody test
□ antistreptolysin O
□ complement levels
□ c-reactive protein
□ cryoglobulin
□ erythrocyte sedimentation rate
□ hepatitis panel (ie, specifically for hepatitis B and C)

Delineating glomerulonephritis based on complement levels may have diagnostic utility (*Figure 5*).

Proteinuria (ie, >3 g per day), hypercholesterolemia, edema, hypoalbuminemia, and fatty casts support a diagnosis of nephrotic syndrome.

The differential diagnosis of nephrotic syndrome is broad, but consists of primary conditions (eg, minimal change disease, membranous disease, focal segmental glomerulosclerosis [FSGS]) and secondary conditions (eg, rheumatologic, amyloidosis, diabetes).

A renal biopsy may be warranted in cases that are suggestive of glomerular disease of unexplained etiology. Nephrologist consultation can aid in the diagnosis and treatment of these relatively uncommon clinical entities.

■ **Vasculature**—Acute kidney injury secondary to vascular compromise can be difficult to diagnosis. Endovascular manipulation followed by AKI raises the possibility of atheroembolic renal disease. Embolic phenomenon, livedo reticularis, hypocomplementemia, and eosinophiluria may help clinicians establish the diagnosis. Microvascular compromise from small to medium-sized vasculitides, including the pulmonary-renal syndromes, requires consideration in the appropriate clinical setting.

The constellation of reduced renal function, fever, mental

Complement Levels
■ **Low**
□ Cryoglobulinemia
□ Hepatitis B or C–related renal disease
□ Lupus nephritis
□ Membranoproliferative glomerulonephritis
□ Postinfectious glomerulonephritis
□ Subacute bacterial endocarditis
■ **Normal* or High**
□ Antiglomerular basement membrane disease†
□ Fibrillary glomerulonephritis
□ Henoch-Schönlein purpura
□ IgA nephropathy
□ Rapidly progressive glomerulonephritis
□ Wegener's granulomatosis

Figure 5. *Categorization of acute renal disease based on complement levels. Differentiating acute glomerulonephritis by complement levels can aid in diagnosis. *Primary nephrotic syndromes (eg, minimal change disease, membranous disease, focal segmental glomerulosclerosis) generally have normal complement levels. †Antiglomerular basement membrane disease is also known as Goodpasture's syndrome.*

status change, anemia, and thrombocytopenia raises the possibility of thrombotic thrombocytopenia purpura, an uncommon, yet serious, form of microvascular renal disease.

Postrenal

Approximately 10% of AKI cases are the result of postrenal causes. Urinary tract obstructions may occur within (eg, stones, tumors) or outside (eg, tumors, retroperitoneal fibrosis) the urinary system.

Ultrasonography has a sensitivity and specificity of up to 95% for detecting such obstructions. In most cases, the treatment of postrenal azotemia involves the prompt surgical resolution of urinary obstructions (eg, Foley catheter).

Special Scenarios

■ **Contrast-induced nephropathy (CIN)**—The third leading cause of AKI in the hospital setting, this condition is defined by an increase in serum creatinine levels that is 25% or higher (0.5 mg/dL) within 72 hours of contrast media administration.[21]

Given the escalating number of procedures and diagnostic studies that require the use of contrast media, a larger percentage of the population is now at risk of CIN.

Associated risk factors for CIN include older age, diabetes, underlying chronic CKD, multiple myeloma, and volume depletion.

Vasomotor alterations and free radical formation are two of the current theories as to how radiocontrast media induces renal failure. The use of hyperosmolar radiocontrast media has been associated with a higher incidence of CIN.[22]

Briguori et al[23] observed reduced risk of CIN in a moderately high-risk patient population using a sodium bicarbonate infusion and N-acetylcysteine concomitantly for prophylaxis. Conversely, a more recent retrospective study[24] showed an increased incidence of CIN when sodium bicarbonate was used for prophylaxis.

Clearly, the most appropriate agents for CIN prophylaxis remain subject to considerable controversy. The use of hypo- to iso-osmolar radiocontrast agents in limited volumes, prehydration (normal saline or bicarbonate-containing solutions), and temporary discontinuation of ACE inhibitors, angiotensin receptor blockers, and diuretics are general principles of CIN prophylaxis.

■ **Sepsis**—Acute kidney injury occurs in approximately 19% of patients with moderate sepsis, 23% with severe sepsis, and 51% with septic shock when blood cultures are positive.[25,26] The combination of AKI and sepsis is associated with a 70% mortality rate, as compared to a mortality rate of 45% among patients with AKI alone.[27]

Basic science research is uncovering the role that nitric oxide synthases, cytokines, chemokines, and adhesion molecules play in AKI when it is associated with sepsis. The use of early goal-directed therapy in sepsis appears to reduce mortality rates among patients with AKI.[28,29]

Less blood pressure variation with continuous modes of hemodialysis suggest that it may be a better treatment option for hemodynamically unstable patients with ARF.[30] To date, however, no data has supported improved survival with continuous RRT (eg, continuous veno-venous hemodiafiltration) as opposed to traditional intermittent RRT.

■ **Hepatorenal syndrome (HRS)**—Patients with cirrhosis and ascites often demonstrate a particular form of kidney injury that is secondary to renal vasoconstriction. Two types of HRS have been described.

Type 1 is characterized by a rapid and progressive impairment of renal function as defined by a doubling of serum creatinine to a level greater than 2.5 mg/dL during 14 days.[31] Type 1 HRS is associated with very low survival expectancy; median survival time is 14 days.[31]

Type 2, by contrast, is a less severe form of HRS and portends a less grave prognosis. In certain patients, triggers like spontaneous bacterial peritonitis or acute gastrointestinal bleeding can be identified.

The diagnostic criteria for HRS include abrupt rise in serum creatinine levels (>1.5mg/dL), absence of other conditions (eg, sepsis, CHF), refractoriness to isotonic saline challenge, and minimal proteinuria.

The treatment of HRS can include trials with midodrine hydrochloride tablets and injectible octreotide; however, orthotopic liver transplantation currently remains the best therapeutic option.

■ **Human immunodeficiency virus (HIV)**—The prevalence of renal disease is increasing among the HIV-infected population,[32,33] likely reflecting increases in renal disease in the general population from diabetes[34] and hypertension,[35] clustering of HIV cases among African Americans,[36] and toxicities of highly active antiretroviral therapy (HAART).[37]

In addition to typical causes of AKI, the differential diagnosis for this syndrome in the HIV-infected population includes the following options among other, less common conditions: HIV-associated nephropathy, HAART-related renal disease, thrombotic thrombocytopenic purpura, FSGS, and membranoproliferative glomerulonephritis.

Nephropathy associated with HIV infection is a rapidly progressing (ie, weeks to months) nephrotic form of kidney disease associated with poorly controlled HIV infection. It occurs almost exclusively in patients of African descent.[38]

A rapidly increasing serum creatinine level, hypertension, and nephrotic-range proteinuria in the setting of a detectable viral load are generally observed. A "collapsing" variant of FSGS on renal biopsy confirms the diagnosis. Highly active antiretroviral therapy is the best method of prevention and treatment—in addition to blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors, angiotensin receptor blockade, or both.

Beside viral-mediated injury, AKI secondary to medica-

tions should be excluded. Tenofovir disoproxil fumarate has been associated with ATN and Fanconi's syndrome. Indinavir sulfate is associated with a crystalline-induced kidney injury. Finally, renal disease resulting from concomitant hepatitis B and C infections should be excluded in all HIV patients.

■ **Nephrogenic systemic fibrosis (NSF)**—An emerging scleromyxedematous condition can occur in patients with diminished renal function after gadolinium exposure. First reported in 1997, incidence rates of NSF are increasing.[39]

This condition causes dramatic skin changes similar to scleroderma. In addition, multisystem organ fibrosis has been reported.[40] Nephrogenic systemic fibrosis carries a high risk of death once systemic involvement supervenes.

Although the majority of incidents occur in patients with end-stage renal disease who are receiving hemodialysis, approximately 10% of these cases involved patients with CKD or AKI.[41] This observation prompted the US Food and Drug Administration[42] to issue a warning to physicians on the use of gadolinium-containing contrast agents in patients with a GFR that is less than 60 mL/min/1.73 m^2.

For now, it is best to avoid using gadolinium for patients with AKI until further information regarding the risks of NSF can be established.

Treatment

As previously noted, treatment plans for patients with AKI are varied and depend on etiologic factors. Prerenal azotemia from volume depletion is usually responsive to isotonic saline repletion. Treatment of ATN requires the discontinuation of nephrotoxic agents, maintenance of optimum hemodynamics, and close surveillance for complications of renal dysfunction (eg, acidosis, electrolyte abnormalities). Postrenal etiologies dictate obstruction removal.

Numerous pharmacologic agents have proven effective in preventing or ameliorating experimental AKI,[43] but none of these substances has been translated successfully to clinical practice. Negative clinical trial experience with insulin-like growth factor 1,[44-47] thyroxine,[48] atrial natriuretic peptide,[49] dopamine,[50] and loop diuretics[51,52] has been reported.

In the absence of effective pharmacotherapeutic options, clinical management of AKI is primarily supportive—with RRT as the central component of care for patients with severe AKI. The generally accepted indications for RRT include volume overload, hyperkalemia, metabolic acidosis, and overt uremic symptoms. Generally, no robust data suggest the benefit of one RRT treatment modality over another (ie, continuous vs traditional intermittent RRT).[30,53]

Conclusion

Acute kidney injury remains a ubiquitous medical condition and is associated with a high rate of mortality. Recent advances in defining and understanding AKI promise to help clinicians better diagnose and treat patients with this burdensome syndrome.

Future research into the mechanisms and pathophysiology of AKI will elucidate the pathways of this complex disease process.

As the clinical management of AKI remains largely supportive, the importance of primary disease prevention is clear.

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