Acute kidney injury (AKI) is a common disease in the acutely ill patient population, as a singular diagnosis or a complication of sepsis, causing significant mortality and morbidity. Progress in diagnosis, treatment, and research in AKI has been limited by the lack of a universally accepted clinical definition. The clinical definition of AKI onset and progression, early diagnostic indicators, and understanding the unique pathophysiology of AKI are requisite to early treatment and management and ultimately positive patient outcomes. This article reviews the advances in defining and staging AKI on the basis of international consensus statements. An update on the most recent concepts affecting renal pathophysiology in AKI is also presented. Current clinical tools used in diagnosing and monitoring AKI, including the development of renal biomarkers, are discussed.

**Keywords:** acute kidney injury, acute renal failure, nursing, renal, sepsis

**ABSTRACT**

Acute kidney injury (AKI) is a common disease in the acutely ill patient population, as a singular diagnosis or a complication of sepsis, causing significant mortality and morbidity. Progress in diagnosis, treatment, and research in AKI has been limited by the lack of a universally accepted clinical definition. The clinical definition of AKI onset and progression, early diagnostic indicators, and understanding the unique pathophysiology of AKI are requisite to early treatment and management and ultimately positive patient outcomes. This article reviews the advances in defining and staging AKI on the basis of international consensus statements. An update on the most recent concepts affecting renal pathophysiology in AKI is also presented. Current clinical tools used in diagnosing and monitoring AKI, including the development of renal biomarkers, are discussed.

**Acute Kidney Injury Definition and Staging**

The concept of renal dysfunction in the acutely ill patient has undergone a major change in the past decade. The term acute renal failure (ARF) has changed to AKI in most of the literature, much like multisystem organ failure is now multisystem organ dysfunction, to reflect a continuum of disease, not a single event. The range of clinical symptoms can be from mild elevations in creatinine level to sustained anuria. The newer staging models recognize update on the definitions, staging, and diagnosis of AKI.

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this continuum to be potentially reversible, with improvement of function. An internationally developed and accepted clinical definition is necessary to evaluate the scope of the problem, promote early detection and diagnosis, evaluate the course of disease in a reproducible manner, and compare research studies, and improve management and outcomes. Although creatinine level and urine output are not highly sensitive indicators of glomerular filtration rate (GFR), they are readily available, clinically tested and verified, and therefore used in most definitions. Because the number of patients with CKD experiencing AKI is increasing, particularly as the population ages and patients survive critical illness, staging criteria also focus on creatinine changes from the patient’s baseline level. The National Kidney Foundation’s stages of CKD are listed in Table 1.

Two international consensus groups have promoted this change in the paradigm. In 2000, the First International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group used a systematic review of available evidence and literature to establish the state in 7 key areas of ARF, including a definition of ARF and a nomenclature of terms. It was proposed that an ARF definition incorporate a stratified classification system and be patient specific by including changes from the patient’s baseline creatinine level.

In 2002, the Second ADQI Conference developed a consensus definition/classification system for ARF, called RIFLE (see Table 2). The acronym RIFLE stands for risk, injury, failure, loss, and end-stage renal disease. This revolutionary system includes 3 levels of renal dysfunction based on changes from the patient’s baseline creatinine level, or urine output over time, to reflect GFR clinical indicators that are readily available at any center. The last two levels—“loss” and “end-stage renal disease”—incorporate clinical outcomes in the staging. Diagnostic levels 1 through 3 are highly sensitive for AKI, whereas outcome levels 4 and 5 are highly specific. RIFLE has undergone rigorous evaluation in a variety of adult populations and has been modified for use in children.

The Acute Kidney Injury Network (AKIN) first met in 2004. This group included the ADQI Group members as well as representatives from international nephrology and critical care societies. Evidence reviewed suggested that even early and minor changes in creatinine level were associated with increased mortality rate. The term acute kidney injury was proposed to represent the entire spectrum of ARF, including early changes in clinical markers. The AKIN acute kidney injury diagnosis criteria is defined as “an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/h for more than 6 hours),” This definition considers the patient’s baseline function and changes in clinical markers within a 48-hour

### Table 1: Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Stage 1: GFR 120-90 mL/min</td>
<td>Screening for risk factors</td>
</tr>
<tr>
<td>Stage 2: GFR 89-60 mL/min</td>
<td>Risk factor screening/reduction</td>
</tr>
<tr>
<td>Stage 3: GFR 59-30 mL/min</td>
<td>Diagnose/treat/slow the progression</td>
</tr>
<tr>
<td>Stage 4: GFR 29-15 mL/min</td>
<td>Treat complications/prepare for RRT</td>
</tr>
<tr>
<td>Stage 5: GFR &lt; 15 mL/min</td>
<td>RRT/renal transplant</td>
</tr>
</tbody>
</table>

### Table 2: RIFLE Criteria for AKI Diagnosis and Staging

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cr increase of 1.5 times or GFR decrease &gt; 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UO &lt; 0.5 mL/kg/h × 6 h</td>
</tr>
<tr>
<td>Injury</td>
<td>Cr increase of 2.5 times or GFR decrease &gt; 50%</td>
</tr>
<tr>
<td></td>
<td>UO &lt; 0.5 mL/kg/h × 12 h</td>
</tr>
<tr>
<td>Failure</td>
<td>Cr increase of 3 times or GFR decrease &gt; 50%</td>
</tr>
<tr>
<td></td>
<td>UO &lt; 0.5 mL/kg/h × 24 h or anuria × 12 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent failure for &gt; 4 wk</td>
</tr>
<tr>
<td>ESRD</td>
<td>Loss of renal function &gt; 3 mo</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; Cr, creatinine; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RIFLE, risk, injury, failure, loss, and end-stage renal disease; UO, urine output.
period (see Table 3). This time period was chosen on the basis of the evidence that even small elevations in creatinine level occurring within 24 to 48 hours are associated with adverse patient outcomes. The 3 stages of AKIN correspond with the first 3 stages of the RIFLE criteria; the last 2 stages of RIFLE were deleted in the AKIN staging system because they constitute outcomes of the disease. The AKIN staging system is more time-sensitive than the RIFLE system.

The American Thoracic Society published an International Consensus Statement on Acute Renal Failure in 2010. The group agreed on changing the terminology from failure but disagreed with the use of the term injury, because an increase in blood urea nitrogen and creatinine level could indicate a change in function but not frank renal injury. The term insufficiency was proposed instead.

The term acute kidney injury is currently the most accepted and used term in the literature for acute renal dysfunction. Both the ADQI and AKIN groups advocate the development and availability of specific, sensitive renal biomarkers for early diagnosis and monitoring of AKI. Clearly, serum and urine biomarkers that detect early changes would indicate the onset of injury and further aid in defining the disease.

Pathophysiology
The kidney normally receives 20% to 25% of cardiac output or approximately 1200 mL/min of blood flow. This flow is normally protected by autoregulation mechanisms, keeping flow and pressure constant and maintaining oxygen delivery, which is necessary for the wide variety of highly metabolic renal functions, underscoring the kidney's vulnerability to ischemic and toxic injury. The 3 major determinants of renal blood flow are cardiac output, renal perfusion pressure, and glomerular hemodynamic factors. Cardiac output is affected by volume status, inotropy, and sodium/water retention. Renal perfusion pressure is influenced by mean arterial pressure, renal artery integrity, and venous outflow. Afferent and efferent arterial vasoconstriction and vasodilatation of the glomerulus ultimately determine glomerular filtration pressure and GFR. Glomerular autoregulation by this means is functional only when systolic arterial pressure is 80 to 170 mm Hg. Renal blood flow and urine formation are also regulated by the renin-angiotensin-aldosterone system, sympathetic nervous system, and antidiuretic hormone from the hypothalamus. Renal endothelial-derived prostaglandins (eg, PGE2) modulate the renal/glomerular vasoconstriction caused by increased sympathetic tone and vasoactive drugs. Loss of these prostaglandins by administration of aspirin, nonsteroidal anti-inflammatory drugs, and other prostaglandin inhibitors can result in severe intrarenal vasoconstriction, decreased GFR, and onset or worsening of AKI.

AKI and Sepsis
Septic AKI accounts for approximately 50% of all AKIs in critically ill patients. The pathogenesis of AKI in sepsis is not fully understood and is more complex than previously thought. It is known that AKI develops early in sepsis; 64% of AKI occurs within 24 hours of septic onset. The lack of histologic evidence limits progress in this area because a renal biopsy in a critically ill patient is prohibitive. Our knowledge in this area is mostly based on animal models.

Several pathways of septic renal injury are currently recognized. Renal cell necrosis is caused by intra- and extrarenal hypoperfusion. Apoptosis, or genetically induced cellular death, is caused primarily by inflammatory mediators and ongoing ischemia. Tumor necrosis factor (TNF) α-1, in particular, has been shown in animal models to upregulate renal apoptosis by binding with TNF receptor 1 on glomerular cells and the TNF receptor 2 sites on renal tubular cells. Cytokines interleukin 1 and 6 also amplify inflammatory and proapoptotic pathways in the kidneys. Thromboxane and other thrombogenic compounds cause platelet adhesion, capillary thrombosis, and ischemia.

<table>
<thead>
<tr>
<th>Table 3: Acute Kidney Injury Network Staging*</th>
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<tbody>
<tr>
<td><strong>Stage 1</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Stage 2</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Stage 3</strong></td>
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<td></td>
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Abbreviations: Cr, creatinine; UO, urine output.
*These stages are from Mehta et al.

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The loss of tubular cell adhesion is the most recently recognized mechanism. In 2000, Schrier and Wang\textsuperscript{20} demonstrated that of the renal tubular cells found in urine after acute tubular necrosis, 40% were metabolically functional. Nitric oxide, which is released systemically in sepsis, has been implicated as a possible cause of loss of tubular cell adhesion to the tubular basement membrane. Kidney injury molecule-1 is a transmembrane protein that is released in proximal tubular damage and loss of cell adhesion. Loss of tubular cellular adhesion results in tubular desquamation, plugging, and backpressure.\textsuperscript{21}

The initial theories of septic injury were based on systemic and intrarenal hypoperfusion, decreasing GFR, ischemia, and cellular necrosis. Recent studies, however, show that the kidney experiences the initial hyperperfusion that occurs systemically in sepsis, but renal injury and apoptosis are significant during this period.\textsuperscript{16,17} Brenner et al\textsuperscript{18} placed thermodilution renal blood flow catheters in 8 intensive care unit patients with septic AKI. The researchers demonstrated that septic AKI occurred despite normal renal blood flow.\textsuperscript{18} Other studies have shown that induction of endotoxin can alter glomerular blood flow and GFR despite normal perfusion pressures. This was initially thought to be due to intrarenal hypoperfusion; however, data now support that this may be due to severe efferent arteriole vasodilatation, resulting in decreased glomerular filtration pressure and GFR. Blood flow in the glomerulus remains high, but the pressure falls because of low glomerular vascular resistance, which might explain why the kidney, during hyperperfusion, experiences a decrease in GFR and urine production.\textsuperscript{16,17} Figure 1 is a flow diagram representing the processes described previously. Although the truth is still evolving in this area, it has become clear that septic AKI is a distinct and different form of this disease. As data become available, the focus in septic AKI may shift from prevention of vasoconstriction and ischemia to prevention of apoptosis and cell exfoliation.\textsuperscript{16,21}

**Fluid Overload/Edema**

A recent prospective study showed that 19% of septic patients with AKI required renal replacement therapy, despite adequate hydration and filling pressures.\textsuperscript{11} Fluid correction, while essential, may not prevent renal injury or progression to renal replacement therapy, particularly in sepsis.\textsuperscript{14} Overhydration and edema can also exacerbate intra-abdominal hypertension and reduce venous outflow pressure, worsening AKI.\textsuperscript{19} An increase in renal interstitial edema caused by overhydration or edema decreases GFR and increases sodium/water retention, further worsening the condition.\textsuperscript{11,17} Although aggressive hydration remains a treatment of nephrotoxic conditions (eg, myoglobinemia, rhabdomyolysis, tumor lysis syndrome, and drug and contrast dye), its use in preventing and treating AKI is not supported.\textsuperscript{11,14} Adequate hydration to optimize hemodynamics is currently recommended.\textsuperscript{11,19}

**Increased Intra-abdominal Pressure**

An increase of more than 12 mm Hg in intra-abdominal pressure in adults has been associated with renal dysfunction.\textsuperscript{22} Increased intra-abdominal pressure exerts pressure on the inferior vena cava and renal veins, with increased renal venous pressure and interstitial edema and decreased GFR. Increased intra-abdominal pressure and abdominal-compartment syndrome are now recognized as “hidden” factors in the pathophysiology of AKI. Renal ultrasonography with Doppler evaluation, including resistive indices of renal blood flow, has become a standard tool for evaluation of renal arterial and venous blood flow and a screening tool for underlying CKD and obstructions or hydronephrosis.\textsuperscript{11,17,19} It is readily available and can be done at the bedside, but it requires an experienced operator. Infrared spectrometry is a continuous, noninvasive method for monitoring tissue oxygenation. It is

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Figure 1: Pathophysiology of acute kidney injury in sepsis. The figure is based on data from Wan et al,\textsuperscript{16} Majumdar et al,\textsuperscript{17} and Schrier et al.\textsuperscript{20}
currently used in clinical trials for monitoring renal perfusion.11,19

**Low Tidal Volume Ventilation**
The Acute Respiratory Distress Syndrome Network has demonstrated that low tidal volume ventilation in critically ill patients reduces mortality rate and the incidence of AKI.16,17 A study by Imal et al in rabbits ventilated with high tidal volumes found increased apoptosis in the kidneys and small intestine, with renal cellular dysfunction in the viable cells. Although little is known about the mechanism, it has been shown that cytokine release during lung overdistention may be a part of this syndrome. Release of the protein Fas ligand is hypothesized to be a part of the apoptotic process.16 Increased tidal volume also increases intrathoracic and abdominal pressures, concurrently decreasing cardiac preload and output and increasing renal venous congestion.11,16,17 Low tidal volumes and plateau pressures of 30 cm H2O or less are recommended to prevent AKI.11

**Tight Glycemic Control**
The van de Berghe group demonstrated that achieving normoglycemic control in critically ill patients reduced mortality rate significantly.24 In addition, it was shown that there was a reduction in mortality rate of patients with AKI who required renal replacement therapy. Subsequent studies showed no reduction in mortality rate of patients with normoglycemia, but there was a reduction in the risk for AKI by RIFLE criteria.24 A possible explanation for this phenomenon is that higher glucose levels cause tubular cell mitochondrial damage. Insulin has been shown to have an anti-inflammatory effect and therefore aids in preventing apoptosis.24,25 Studies, however, have shown that hypoglycemic patients have a higher mortality rate than normoglycemic patients; “tight” control in an unstable patient can often be challenging. The literature supports normoglycemia to prevent AKI.11,17

**Diagnosis**
**Estimating Glomerular Filtration Rate**
Equations or formulas are commonly used for estimating GFR in AKI (Table 4), particularly for pharmacokinetics and drug dosing. These formulas usually extrapolate GFR as a function of middle-weight molecular clearance from serum to urine such as creatinine. Age, body weight and mass, race, gender, muscle mass, total body water, and diet, which affect the generation and distribution in the body fluid compartments of creatinine, affect the accuracy of these equations.2,8 Of note, many of these factors are altered in acute illness. Each formula, listed in Table 4, uses different combinations of these factors in estimating GFR.

The Cockcroft-Gault formula is most commonly used and provides an estimate of creatinine clearance (CrCl). It was developed in 1976 with a study population of 279 white men with a mean CrCl of 73 mL/min. The assumption in using this formula is that serum creatinine is at steady state, and it has been shown to be less accurate in obese patients.26 In 1979, the Modification of Diet in Renal Disease formula was developed with patients with CKD. This formula estimates GFR and takes into account the difference in CrCl that exists in patients of African descent.27 The Jelliffe formula was developed primarily for monitoring drug levels and is used in the setting of changing kidney function because it uses 2 serum creatinine measurements at least 1 day apart.24,29 The modified version has the creatinine adjusted for the patient’s body surface area and fluid balance. It is proposed that because it evaluates creatinine changes over time and adjusts for fluid status, it may be the preferred formula for pharmacokinetics and drug dosing.29

Bouchard et al compared these methods with urine CrCl in nondialyzed, critically ill patients with changes in serum creatinine level over a 3- to 7-day period. Estimated GFR by Cockcroft-Gault, Modification of Diet in Renal Disease, and Jelliffe formulas overestimated urinary CrCl by 80%, 33%, and 10%, respectively, and the modified Jelliffe formula under-

### Table 4: Formulas for Calculation of Renal Function

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>Estimated CrCl = (140 - age) × Mass (in kg) ÷ 0.85 if woman ÷ 0.72 × serum creatinine (in mg/dL)</td>
</tr>
<tr>
<td>MDRD</td>
<td>CrCl = 186 × (serum creatinine - 1.154) × (age - 0.203) ÷ 1.210 if black ÷ 0.742 if woman</td>
</tr>
<tr>
<td>EGFR</td>
<td>Modified Jelliffe: CrCl = 0.9 × ([98 - 0.8 × [age, 20]] ÷ serum creatinine</td>
</tr>
</tbody>
</table>

Abbreviations: CrCl, creatinine clearance; EGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

*These formulas are from the National Kidney Foundation, Bouchard et al, and Levy et al.*

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estimated GFR by 2%. Although accuracy in estimating GFR varies, these equations remain a readily available, noninvasive, and cost-effective method for estimating GFR. However, these formulas depend on measurements of creatinine level, usually assumed to be in “steady state” (not the usual condition in acutely ill patients), and that has been shown to be a non-specific, relatively insensitive marker for AKI. The formulas do not provide “early warning” of AKI when intervention may be the most effective in aborting progression of disease.

Fractional Excretion of Sodium and Urea

Comparison of levels of small- and middle-weight molecular markers in serum and urine can also aid in differential diagnosis of AKI, particularly between pre- and intrarenal pathology. The fractional excretion of sodium (FENa) evaluates the difference in serum and urine sodium against a more “stable” marker, creatinine. Fractional excretion of sodium is calculated using the following formula: (urine Na × plasma Cr)/(plasma Na × urine Cr) = FENa%. A FENa of less than 1% is consistent with renal tubules actively conserving sodium, as in prerenal failure. A FENa of more than 1% tends to reflect that the tubules are not actively conserving sodium, as in acute tubular necrosis, and predicts this with 80% accuracy. Although helpful in determining fluid status and differential diagnosis of pre- and intrarenal failure, FENa is affected by the use of diuretics, alkalosis, CKD, and glycosuria. The fractional excretion of urea can be used instead of FENa in these conditions. Urea is dependent on intrarenal pressure for removal instead of secretion and is not normally affected by alkalosis or diuretics. The fractional excretion of urea can be calculated by substituting serum and urea measurements in the FENa calculation. In the normal, well-hydrated patient, the value is 50% to 65%. In patients with AKI, a value of less than 35% supports prerenal azotemia and greater than 50% is consistent with acute tubular necrosis or intrinsic renal disease. Although these formulas are helpful in differential diagnosis of pre- and intrarenal states and monitoring of fluid administration, they do not serve as early indicators or monitors of renal injury.

Renal Biomarkers

Several serum and urine chemical markers of renal injury are currently under investigation for clinical use. Cystatin C is a cysteine protease inhibitor produced by all nucleated cells in the body at a constant rate. It is freely filtered by the glomerulus and reabsorbed by the tubules. This marker reflects sudden changes in GFR earlier and more accurately than creatinine. Its production is constant in the body, and it is not affected by infection, diet, gender, age, or race, as are urea and creatinine. If confirmed as a reliable indicator of renal injury, it is anticipated that cystatin C will replace serum creatinine in monitoring critically ill patients.

Neutrophil gelatinase-associated lipocalin is found in neutrophils and epithelial cells, including those of the proximal tubules. This marker rises early and dramatically in AKI, prompting the designation of “tropinin for the kidney.” It is found in substantial amounts in both serum and urine in AKI patients. In a study by Bagshaw et al, patients with septic AKI demonstrated significantly higher serum levels of neutrophil gelatinase-associated lipocalin than did patients with nonseptic AKI. This may lead to a method of differentiating septic versus nonseptic AKI, allowing the clinician to tailor treatment of these different etiologies.

Other urine biomarkers include interleukin 18, a potent cytokine, and kidney injury molecule-1. Kidney injury molecule-1 is released with loss of tubular cell adhesion, resulting in sloughing of tubular cells, tubular blockage, and congestion. In addition to being a marker of AKI, this molecule may modulate or participate in renal cellular repair. Note that these markers tend to lose their specificity in sepsis and oliguric states; correlative studies are needed to interpret their significance in these conditions. Additional validation in multiple-patient populations of these specific, sensitive renal biomarkers is in progress.

Conclusion

Acute kidney injury remains a complex disorder with an apparent differentiation in pathology between septic and nonseptic forms of the disease. Having common definitions and diagnostic tools aids in the research and, ultimately, the management of AKI. Although more study is still required, progress in this area has been steady over the last decade, with purposeful international collaboration.

REFERENCES


