Sepsis-Associated Acute Kidney Injury

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Summary: Acute kidney injury (AKI) is an epidemic problem. Sepsis has long been recognized as a foremost precipitant of AKI. Sepsis-associated AKI (SA-AKI) portends a high burden of morbidity and mortality in both children and adults with critical illness. Although our understanding of its pathophysiology is incomplete, SA-AKI likely represents a distinct subset of AKI contributed to by a unique constellation of hemodynamic, inflammatory, and immune mechanisms. SA-AKI poses significant clinical challenges for clinicians. To date, no singular effective therapy has been developed to alter the natural history of SA-AKI. Rather, current strategies to alleviate poor outcomes focus on clinical risk identification, early detection of injury, modifying clinician behavior to avoid harm, early appropriate antimicrobial therapy, and surveillance among survivors for the longer-term sequelae of kidney damage. Recent evidence has confirmed that patients no longer die with AKI, but from AKI. To improve the care and outcomes for sufferers of SA-AKI, clinicians need a robust appreciation for its epidemiology and current best-evidence strategies for prevention and treatment.
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Acute kidney injury (AKI) is a very common problem in critically ill patients. With the integration of consensus AKI definition criteria from Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE), Acute Kidney Injury Network (AKIN), and, most recently Kidney Disease Improving Global Outcomes (KDIGO), AKI incidence in adult intensive care unit (ICU) settings has been reported to range between 16% and 67%.[1–11] Several pediatric ICU studies have reported similarly high incidence rates.[12,13] Unfortunately, mounting evidence suggests that AKI incidence is increasing. In a large 10-year cohort that included more than 90,000 patients from more than 20 ICUs, AKI incidence increased by 2.8% per year.[3] A longitudinal pediatric study showed a parallel increase in reported AKI incidence.[14] The presence of AKI has been associated consistently with increased morbidity and mortality for both adults and children. Furthermore, because no singular effective therapy for AKI has been identified, appreciation of AKI risk and early detection of injury coupled with initiation of appropriate supportive care and harm avoidance remain the mainstay of therapy. The evidence indicates that people are no longer just dying with AKI, but from AKI.[15]

Sepsis is a significant primary driver of critical illness. The incidence of sepsis or septic shock is high and increasing. A 22-year retrospective analysis of hospitalization records in the United States found an 8.7% annual increase for a sepsis diagnosis.[16] The incidence of severe sepsis between 2004 and 2009 showed an average annual increase of 13%.[17] Although the overall sepsis-related mortality rate is decreasing (now approaching 18%-25%), the standardized mortality rate for septic patients continues to be significantly higher than the overall ICU standardized mortality ratio.[18,19] In addition, global estimates suggest that the associated effects of sepsis are significant and encompass all aspects of ICU-related morbidity—including prolonged length of stay, ventilation, secondary infections, and mortality, along with long-term survivorship issues.[19–22] Despite many studies of multitudes of patients and randomized controlled trials of specific therapies (eg, activated protein C), early disease recognition, rapid fluid resuscitation, and early administration of antibiotics represent the only therapies leading to improved outcomes for patients with sepsis.[23]

Sepsis is the most common contributing factor for the development of AKI. In adult and pediatric data, sepsis accounts for 26% to 50% of all AKI in developed nations, compared with 7% to 10% of primary kidney disease–associated AKI.[24–28] Clinical and basic science evidence indicate that sepsis-associated AKI

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(SA-AKI) is distinct from AKI without sepsis, driven by a number of characteristic pathophysiological mechanisms, carrying a unique profile of timing (onset, duration), and being associated with different short- and long-term outcomes. Given the global and pervasive impact of AKI and sepsis, an understanding of SA-AKI is required for the nephrologist and the intensivist to appropriately devise detection, treatment, and follow-up strategies.

In this review, we present a broad-scale characterization of SA-AKI, supported by clinical and laboratory evidence. By describing the who, what, when, where, and how, we provide the reader with evidence showing AKI epidemiology, disease burden and outcomes, pathophysiological mechanisms, diagnostic strategies, and potential preventative and therapeutic strategies.

SA-AKI: WHO SUFFERS INJURY AND IS AT HIGHEST RISK?

General Epidemiology

Sepsis-associated AKI occurs at a high incidence rate in critically ill patients (Table 1). A large study from 57 adult ICUs in Australia and New Zealand identified SA-AKI in 11.7% of 120,123 patients.[24] The Beginning, Ending Supportive Therapy for the Kidney, a large prospective observational study of more than 29,000 patients, reported an AKI incidence of 5.7%, with SA-AKI being the highest associated etiology (47.5%).[25] Analysis of 276,731 admissions to 170 adult critical care units of the UK Intensive Care National Audit and Research Center identified concurrent sepsis and AKI in 8,246 ICU admissions in the first 24 hours.[28] Retrospective studies in primarily sepsis cohorts also have reported a high concurrence of SA-AKI. More than 60% of 4,532 adult patients with septic shock from 1989 to 2005 suffered AKI.[29] Meanwhile, in another cohort, AKI was present in 17.7% of 722 patients admitted to an ICU specifically for infectious disease.[30]

Sepsis carries a strong association with the development of AKI in critically ill children. Infection was identified as an independent predictor of AKI in a large pediatric cohort of 2,106 critically ill children (AKI incidence, 18%).[31] A 10-year longitudinal retrospective analysis reported sepsis as a leading cause of AKI in 180 children.[32] A prospective multicenter study from Turkey reported sepsis as a leading cause of AKI in 18% of 472 patients.[33] Similarly, sepsis was an independent risk factor for the development of AKI in a retrospective observational study from India.[34]

The severity of sepsis increased the incidence of AKI. Multiple studies have reported a stepwise increase of AKI incidence according to sepsis

Table 1. Summary of Epidemiologic Studies of SA-AKI

Study	Year	Design	ICU Type(s)	Population (n)	AKI Definition	SA-AKI Incidence (%)
Sood et al[46]	2014	Prospective observational, multicenter	Mixed	Septic shock (5443)	RIFLE criteria	77.6
Alkandari et al[31]	2011	Retrospective, two centers	Pediatrics	AKI (2106)	AKIN criteria	10.3
Lopes et al[36]	2009	Retrospective, single center	Infectious disease	Sepsis (315)	AKIN criteria	31.4
Bagshaw et al[29]	2009	Retrospective, multicenter	Mixed	Septic shock (4523)	RIFLE criteria	64.0
Daher et al[30]	2008	Retrospective, single center	Infectious disease	Sepsis (722)	RIFLE criteria	20.3
Cruz et al[27]	2007	Prospective observational, multicenter	Mixed	AKI (2164)	RIFLE criteria	25.6
Bagshaw et al[25]	2007	Prospective observational, multicenter	Mixed	AKI (120123)	RIFLE criteria	32.4
Oppert et al[39]	2007	Prospective, cross-sectional, 1-day prevalence	Mixed	Severe sepsis and septic shock (401)	SCr × 2 or UO, <0.5 mL/kg/h × 4 h	41.4
BEST Kidney[25]	2007	Prospective observational, multicenter	Mixed	AKI (1753)	Urea, >30 mmol/L or UO, <200 mL/12 h or RRT	47.5
Lopes et al[36]	2007	Retrospective, single center	Infectious disease	Sepsis (182)	RIFLE criteria	37.4
Yegenaga et al[40]	2004	Prospective observational, single center	Mixed	Sepsis/SIRS (257)	SCr, >177 mmol/L	11.0
Hoste et al[38]	2003	Retrospective, single center	Surgical	Sepsis (185)	SCr, >177 mmol/L	16.2

Abbreviations: BEST, Beginning, Ending Supportive Therapy for the Kidney; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome; UO, urine output.

severity.[35–37] In a cohort of 315 patients, AKI incidence increased significantly according to sepsis severity (4.2% for sepsis, 22.7% for severe sepsis, and 52.8% for septic shock).[37]

High-Risk Populations

Populations at high risk of SA-AKI have been identified. Elderly patients carry a higher incidence rate of SA-AKI.[24,25,36,38] In addition, females were found to be affected more commonly.[29] Baseline comorbidities, specifically chronic kidney disease, diabetes mellitus, heart failure, malignancy, and liver disease increase patients' susceptibility to SA-AKI.[24,25,29,39] Sources of sepsis, in particular, bloodstream infection, abdominal and genitourinary sepsis, and infective endocarditis, are associated with a higher likelihood of developing AKI. Similar to the poor outcome of patients with sepsis, delayed administration of appropriate antimicrobial therapy was shown to be an independent predictor of the development of AKI. Incremental delays in antimicrobial delivery after the onset of hypotension showed a direct relationship with the development of AKI.[29]

SA-AKI: WHAT IS THE LEVEL OF ASSOCIATED ILLNESS, COST, AND OUTCOMES?

Severity of Illness

Compared with nonseptic AKI, SA-AKI is associated with a higher acuity of illness. Patients with more severe AKI by RIFLE criteria were more likely to have Acute Physiology and Chronic Health Evaluation II (APACHE II) scores higher than 45 (Risk, 45%; Failure, 70%).[29] Similarly, sequential organ failure assessment scores were found to be higher in patients with SA-AKI compared with nonseptic AKI.[25] Compared with nonseptic AKI, SA-AKI patients have more abnormalities in markers of inflammation and blood biochemistry. Similarly, SA-AKI patients are more likely to receive mechanical ventilation, hemodynamic support with vasoactive therapy, and receive larger volumes of fluid for resuscitation.[21,25,29,38]

Severity of AKI

AKI is often more acute and more severe in patients with sepsis compared with nonseptic AKI. SA-AKI patients have greater changes in serum creatinine levels from baseline and more SA-AKI patients fulfill severe AKI by RIFLE-Injury and RIFLE-Failure.[24] The relative proportion of SA-AKI patients fulfilling criteria for RIFLE-Injury (16.3%) and RIFLE-Failure (9.6%) were significantly greater than patients with nonseptic AKI (12.6% and 5.0%, respectively).[24] Patients with SA-AKI often have more pronounced oliguria and achieve greater degrees of positive fluid balance and overload compared with patients with neither AKI nor sepsis.[20,24,28,40] In addition, there is an association between the increasing severity of sepsis and the severity of AKI. In one cohort, the proportion of patients supported with renal replacement therapy (RRT) increased from 24% to 89% as patients progressed from sepsis to septic shock.[35]

Cost of SA-AKI

The annual cost of sepsis and AKI in the United States is noteworthy. Sepsis alone carries a significant health care burden, with an estimated average cost of $22,100 US per case and an annual total cost of $16.7 billion US dollars nationally.[20] On the other hand, AKI patients have an approximately $9,000 US increase in hospital costs compared with hospitalized patients who did not develop AKI.[41] Moreover, AKI in critically ill patients is associated with prolonged mechanical ventilation, a longer ICU stay, and increased rates of rehospitalization.[42–44] The cost of sepsis concurrent with AKI is significant.

Outcomes: Length of Stay, Renal Recovery, and Mortality

Sepsis-associated AKI is associated strongly with a poor prognosis. Observational studies consistently have reported significantly worse outcomes with SA-AKI versus nonseptic AKI or sepsis alone.[24,25,29,38,39] Length of stay is longer in patients with SA-AKI versus AKI without sepsis or sepsis alone. Septic patients developing AKI were found to have twice the duration of ICU stay compared with septic patients without AKI.[38] Similar findings from a larger cohort found SA-AKI patients to have longer ICU and hospital stays compared with nonseptic AKI or sepsis alone. Moreover, there was a stepwise increase of length of stay according to AKI severity. The median ICU length of stay increased from 3.1 to 4.8 days as SA-AKI patients progressed from RIFLE-Injury to RIFLE-Failure.[24] Recovery of renal function was similar for patients with SA-AKI versus AKI without sepsis. Complete renal function recovery occurred in 95.7% of 315 SA-AKI patients, with a mean time for complete recovery of 10.1 $\pm$ 8 days.[37] Interestingly, the Beginning, Ending Supportive Therapy for the Kidney study showed similar rates of dependence on chronic RRT for septic AKI (5.7%) versus nonseptic AKI (7.8%) patients.[24] Both ICU and in-hospital mortality rates were significantly higher for patients with SA-AKI compared with patients with AKI without sepsis (ICU mortality rate, 19.8% versus 13.4%; in-hospital mortality rate, 29.7% versus 21.6%).[24] In

addition, there was a stepwise increase for ICU, in-hospital, and 90-day mortality rates in septic AKI patients reported when patients were stratified by AKI severity defined by the RIFLE criteria.[28,29] Mortality was significantly higher in patients with SA-AKI for AKI-AKIN stage 3 (64.1%) compared with AKI-AKIN stage 1 (34.6%).[37]

SA-AKI: WHEN ARE PATIENTS SUFFERING INJURY AND WHAT TIME FRAME PORTENDS RECOVERY?

Timing of SA-AKI

Observational data suggest that injury during SA-AKI occurs early in the course of critical illness and after ICU admission. Separate studies have reported that AKI occurred within 24 hours of ICU admission for adult patients with sepsis.[29,45] In a large recent cohort, 68% of 5,443 patients with septic shock had evidence of AKI within 6 hours after presentation.[46]

Patients who showed evidence of kidney function recovery or improvement in their RIFLE category within 24 hours after presentation had better survival compared with those with no AKI or persistent AKI beyond 24 hours. Younger patients, patients who received early appropriate antimicrobials, patients with lower APACHE II scores, and those patients community-acquired infection were shown independently to be more likely to have early recovery from AKI within 24 hours.[46] The development of AKI later during the course of an episode of sepsis has been associated with worse clinical outcome and increased mortality rates (76.5% compared with 61.5% in early AKI).[45]

SA-AKI: WHERE IS THE INJURY OCCURRING?

General Pathophysiology

Our current understanding of the pathophysiology driving AKI mediated by sepsis is incomplete[47,48] (Fig. 1). Sepsis-mediated hypoperfusion leading to tubular necrosis traditionally has been cited as the primary pathophysiology for SA-AKI, however, mounting evidence has challenged this paradigm.[49,50] Numerous drivers for injury now are recognized as playing a role in SA-AKI, including ischemia-reperfusion injury to the glomerulus, inflammation of specific parts of the nephron, hypoxic and/or oxidant stress, cytokine- and chemokine-driven direct tubular injury, and tubular and mesenchymal apoptosis.[51] The reader is referred to the other articles in this issue.

Alterations in Systemic and Renal Hemodynamics

Sepsis inconsistently leads to aberrant renal perfusion. For a number of reasons, there are a paucity of human data assessing renal blood flow (RBF) in septic patients. Renal vein thermodilution measurement of RBF in 8 septic critically ill patients did not show hypoperfusion to the glomerulus consistently.[52] In these patients, decreases in glomerular filtration rate did not correlate with changes in RBF and vice versa. Multivariate analysis in a systematic review of 159 animal studies, a majority of which (62%) reported decreased renal blood flow during sepsis, showed that RBF is predicted only by sepsis-induced changes to cardiac output (ie, low cardiac output).[50] In an ovine model of *Escherichia coli* sepsis, sepsis conferred a period of hyperdynamic RBF for 48 hours after *E coli* infusion, which was attributed to increased cardiac output and renal vasodilatation.[53] A separate randomized placebo ovine sepsis model studied the selective vasoconstriction of the efferent arteriole using an angiotensin II infusion. The hyperdynamic septic subjects showed increased RBF associated with decreased creatinine clearance and urine output. Subsequently, angiotensin II infusion resulted in a reduction of RBF and improved creatinine clearance (70%) and urine output (7-fold increase) compared with placebo.[54] Overall, RBF seems to be less contributory to renal perfusion during sepsis unless cardiac output is affected. The primary aberration occurring early during sepsis may be glomerular perfusion pressure, underscoring the importance of how intraglomerular hemodynamics regulate glomerular filtration rate (see article by Prowle et al in this issue).

Immune- and Inflammatory-Mediated Injury

Sepsis triggers a systemic cytokine-chemokine response. A biphasic profile of immune activation followed by suppression is shown, and the systemic effects of sepsis have the potential to lead to end-organ injury in the kidney. Acute tubular necrosis (ATN) is classically used to describe the cellular effects of sepsis driven by both ischemia-reperfusion injury and cytokine-mediated inflammation. However, this terminology is dated and likely should be supplanted by modern clinical descriptions of AKI. This notion is supported by autopsy studies showing that only 22% of 117 patients with clinically defined septic AKI-ATN had histopathologic features suggestive of acute tubular necrosis on biopsy.[49]

Cellular Injury

Tubular cellular injury contributes to the propagation of AKI during sepsis. A number of different causal mechanisms appear to be involved, but tubular necrosis, traditionally cited as the major cellular switch for injury, is not supported by the available experimental evidence.

Renal tubular apoptosis in response to the stress of systemic sepsis now is cited as a potential contributing

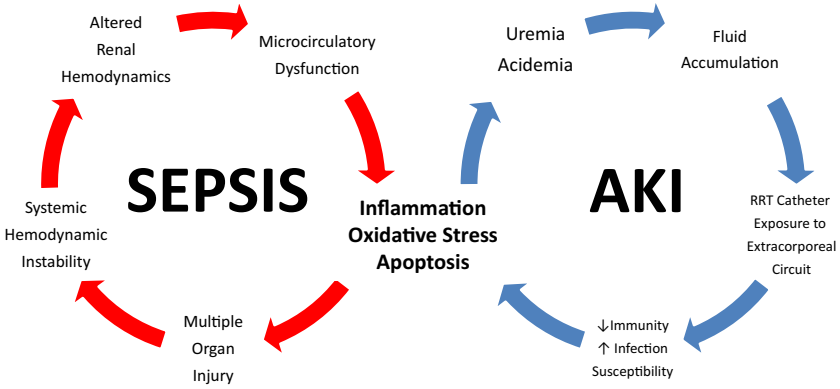

Figure 1. Sepsis and AKI pathophysiological interaction in SA-AKI. Reprinted with permission from Romanovsky et al.[92]

mechanism of injury in SA-AKI. In a side-by-side experimental comparison of murine models of SA-AKI versus ischemia-reperfusion (using cecal ligation puncture model), renal cell apoptosis was more prominent on renal histology in the SA-AKI mice with minimal tubular injury or inflammation. In addition, the SA-AKI mice showed increased renal interleukin-10 expression and proliferation of regulatory T cells. Inhibition of caspase-3 modulated the severity of AKI, supporting a mechanistic role for apoptosis in propagating injury.[55] In a porcine model of fecal peritonitis, renal tubular cells showed vacuolization and injury to cellular brush borders but no evidence of necrosis (Fig. 2).[56] A comparison of postmortem kidney biopsy specimens from 19 patients with septic shock versus trauma and nonseptic patients showed an increase in renal tubular cell apoptosis and leukocyte infiltration in the septic group. Tubular apoptosis was not observed in the nonseptic group.[57]

Cellular hypoxia is a molecular driver of injury during SA-AKI. Tissue hypoxia in the kidney during sepsis may be defined by inflammation, changes in intrarenal nitric oxide, nitrosative stress or oxygen radical homeostasis, and dysregulation.[58,59] Down-regulation of mediators of oxidative phosphorylation occurs during sepsis and protection of mitochondrial respiration may mitigate renal injury during sepsis.[60] In a model of lipopolysaccharide-induced endotoxemic AKI, reactive nitrogen species and reactive oxygen species (ROS) were overexpressed in the renal cyto-

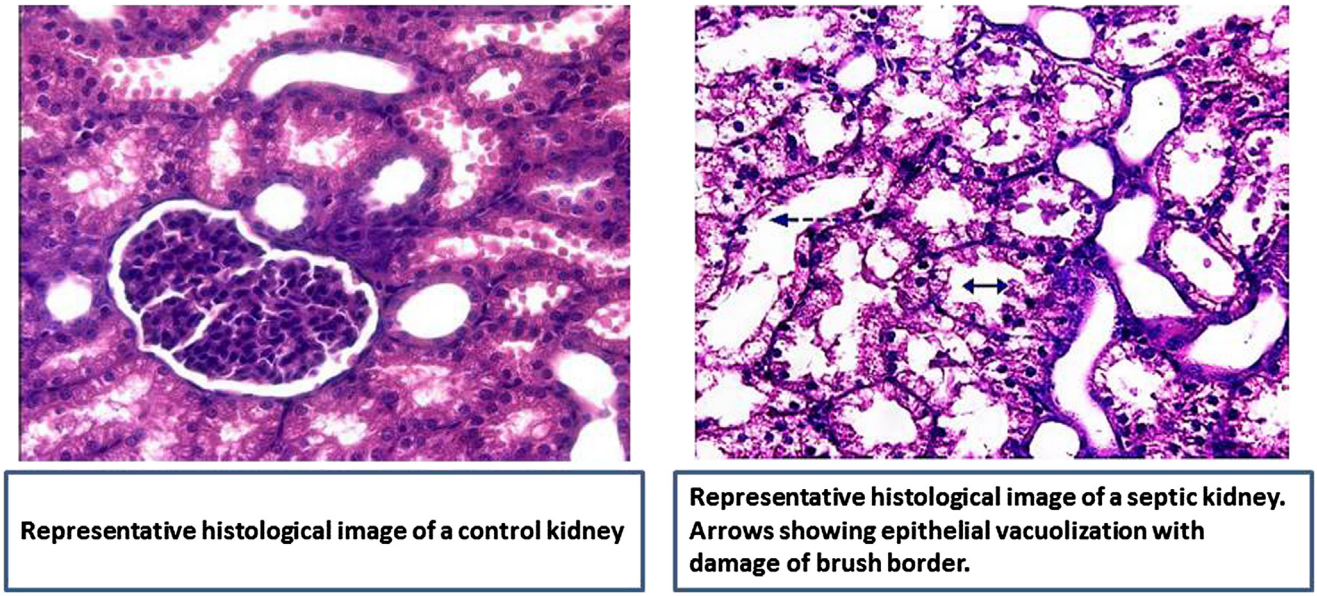

Figure 2. Porcine sepsis model does not show renal tubular necrosis. In a porcine model of fecal peritonitis, representative histopathologic cross-sections of renal tubules shows tubular vacuolization, a precursor of cellular apoptosis, but no evidence of necrosis. (A) Representative histologic image of a control kidney. (B) Representative histologic image of a septic kidney. Arrows show epithelial vacuolization with damage of brush border. Reproduced with permission from Chvojka et al.[56]

solic compartment, implicating mitochondrial and oxidative dysfunction during sepsis. The conclusion of this study suggests that injury occurs during SA-AKI from dysregulation of transcriptional events, ROS signaling, mitochondrial activity, and metabolic orientation such as apoptosis (see articles by Parikh et al and Kumar et al in this issue).[61]

SA-AKI: HOW CAN DIAGNOSTICS AND THERAPEUTICS MOVE FORWARD TOWARD IMPROVING OUTCOMES?

Risk Recognition and Early Diagnosis

The severity of injury and poor outcomes associated with SA-AKI worsen with delayed recognition of injury. Because no singular effective therapy has been uncovered, early initiation of supportive care targeting the drivers of injury are the mainstays of therapy. The activation of such support relies on risk recognition and early diagnosis of injury. Urinary indices and urine biochemistry, traditionally used to classify AKI, are inadequate to delineate subtypes of AKI during sepsis. In a study of 83 critically ill adults, fractional excretion of sodium and urea (FeNa and FeU) were not significantly different in patients with SA-AKI versus AKI without sepsis.[62] In addition, FeNa, FeU, and urine sodium (UNa) showed poor discrimination for worsening AKI, the need for RRT, and mortality. In broader study of urinary biochemistry and microscopy performance for the prediction of SA-AKI, very little consistency exists for the timing of urinary tests and outcomes measured, much less the strength of test results and AKI.[63,64] Urinary sediment tests also were inconclusive and variable between studies of sepsis and AKI.

Unfortunately, detection of SA-AKI continues to rely on acute and relative changes in serum creatinine level, which is known to carry significant limitations, particularly in pediatrics. Novel biomarkers already have shown an ability to identify SA-AKI before changes in serum creatinine levels. Plasma and urine neutrophil gelatinase-associated lipocalin (NGAL) levels were significantly higher at 0, 12, and 24 hours in 83 patients with SA-AKI compared with patients with nonseptic AKI.[65] In 150 critically ill adult patients, urinary NGAL showed significant discrimination for AKI in patients with sepsis (area under receiver operating characteristic curve [AUC], 0.80). Although plasma NGAL level increases in patients with sepsis, levels were associated significantly with the renal subscore of the sequential organ failure assessment score in critically ill adults.[66] In a separate prospective evaluation of 150 septic patients, urinary netrin-1 and kidney injury molecule-1 were increased within 3 hours of admission for patients with AKI.[67] In initial studies, serum NGAL levels showed only marginal prediction for AKI in children with sepsis (AUC, 0.68). A recent study, however, showed the ability of NGAL to improve the prediction of severe AKI afforded by the clinical context model of the renal angina index (AUC increased from 0.72 to 0.84).[68]

Markers specific for sepsis-induced cellular injury may carry high predictive precision for SA-AKI. An increase of E-selectin, typical of inflammatory and endothelial activation, is associated with future AKI in a longitudinal evaluation of patients after sepsis.[69] In a large multicenter study of critically ill adults, cell-cycle arrest markers tissue inhibitor of matrix metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFB7) showed superior discrimination for AKI compared with other novel biomarkers such as NGAL, interleukin-18, liver type–fatty acid binding protein, and kidney injury molecule-1 (AUC, 0.80 for TIMP-2/IGFBP7 versus <0.72 for the others).[70] In this study, the predictive performance of TIMP-2/IGFBP7 for AKI was increased further in patients with sepsis (AUC, 0.82).

Risk-stratification methodologies such as the concept of renal angina have shown the ability to enhance prediction of severe SA-AKI.[71] The Renal Angina Index mentioned earlier, a combination of demographic factors and changes in creatinine clearance or fluid accumulation, provides a composite score that has

Table 2. The Renal Angina Index for Pediatric Patients (58)

Risk				Injury		
Demographics	**Class**	**Score**		**↓ eCCl**	**↑ FO**	**Score**
ICU admission	Moderate	1		0	<5%	1
Transplantation	High	3	×	1%-24%	≥5%-10%	2
Ventilation + inotropy	Very high	5		25%-49%	≥10%-15%	4
				≥50%	≥15%	8

The renal angina index is calculated by multiplying the patient risk score by the injury score. The higher score of either of the injury criteria, eCCl or FO, is used. A Renal Angina Index product of ≥8 fulfills the renal angina classification. Transplantation refers to solid organ or stem cell transplantation.

Abbreviations: eCCl, estimated creatinine clearance by the Schwartz formula[91]; FO, percentage of fluid overload normalized for ICU admission weight.[75]

a very high negative predictive value for AKI development in patients with sepsis[72] (Table 2). The Renal Angina Index model also shows improvement after the incorporation of novel kidney damage biomarkers.[68] Prospective analysis of the predictive performance of these novel damage-specific biomarkers in both blood and urine for SA-AKI currently is under investigation. Use of specific biomarkers that are indicative of specific types of injury has been purported by the 10th Consensus Meeting of the Acute Dialysis Quality Initiative as an objective of AKI research.[73]

Renal Replacement Therapy

Renal support therapy has been used for the treatment of SA-AKI. Although criteria for RRT initiation is highly controversial, some retrospective data suggest initiation before the onset of overt complications of AKI and the accumulation of a significant amount of fluid overload may be associated with improved survival.[74,75] The ideal modality to support critically ill septic patients with AKI remains unresolved. Continuous renal replacement therapy (CRRT) is used most commonly in unstable critically patients because of its adaptability to patient condition and better physiologic and hemodynamic hemostasis control. Although no definitive evidence has shown a survival advantage with one particular modality,[76] recent data have suggested that initial support with CRRT may better facilitate recovery of kidney function to RRT independence and reduce the long-term risk of incident chronic kidney disease.[77,78] Despite early data by Ronco et al[79] suggesting a potential benefit from higher-intensity dose dialysis (35-45 mL/kg/h), subsequent evidence from 2 large multicenter randomized trials (Randomized Evaluation of Normal Versus Augmented Level Renal Replacement Therapy [RENAL] and ATN: Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study) showed no added benefit of higher-intensity dose RRT compared with lower-intensity dose RRT, with fewer metabolic complications.[80,81] In addition, in both the RENAL and ATN studies, there were no significant difference in the odds ratios (ORs) for mortality in patients with sepsis who received higher- versus lower-intensity RRT. In the RENAL study, high- versus low-intensity RRT conferred an OR for death by 90 days of 0.84 (95% CI 0.62-1.12), whereas in the ATN study intensive versus less-intensive therapy conferred an OR for death at 60 days of 1.19 (0.88-1.62).[80,81] Although some data have suggested that CRRT may have a potential immunomodulatory effect in sepsis, the hIgh VOlume in Intensive caRE (IVOIRE) study investigated high-volume hemofiltration in septic shock patients with AKI and found no survival or clinical benefits.[82] Overall, the evidence for different blood purification techniques in improving sepsis outcome by removing apoptotic and proinflammatory factors is evolving (see article by Forni et al in this issue).[83]

Targeted Molecular and Cell-Based Therapy

Because the pathogenesis of SA-AKI now is seen as a multifactorial process involving apoptotic, immune, and inflammatory processes, novel perspective medical therapies directed at these pathways have emerged and could be of potential therapeutic value. Targeting the apoptotic pathway with caspase inhibitors and suppressing inflammatory cascades have shown some promising results in experimental models. Lee et al[55] found that treating mice in an experimental septic model with caspase 3 and interleukin-10 inhibitors had some protective effect against the development of septic AKI in mice. Similar findings were observed in an earlier rat model with glycerol-induced AKI, early caspase inhibition–attenuated apoptosis and inflammation processes, and reduced renal function impairment.[84] Other therapeutic agents such as ghrelin,[85] low-dose vasopressin,[86] adenosine-receptor agonists,[87] and erythropoietin[88] have shown some renal anti-inflammatory and apoptosis-suppressing qualities. Modulation of mitochondrial oxidative phosphorylation through antioxidants also may be of benefit in SA-AKI because hypoxia-induced ROS and nitric oxide synthase during sepsis may contribute to renal tubular injury.[89] Recent experimental data and evidence from a small pilot trial has shown potential for the enzyme alkaline phosphatase to improve outcome in SA-AKI by favorably modulating the immune response.[90] Further evidence assessing their beneficial effect in SA-AKI patients is needed (see article by Swaminathan et al in this issue).

CONCLUSIONS

AKI is a significant clinical challenge for clinicians. Although SA-AKI is likely a unique subset of all AKI, our capability to effectively intervene therapeutically has been paralyzed largely by an incomplete understanding of its complex pathophysiology. The preponderance of evidence imply that SA-AKI contributes to a high burden of morbidity and mortality in both children and adults with critical illness. To date, no singular effective therapy has been developed to alter its natural history. However, advancements have been made across several fronts including the development of robust and validated tools for clinical risk identification such as the concept of renal angina, discovery of novel damage biomarkers to enable early detection of injury, use of informatics and clinician information systems to modify clinician behavior by providing decision support and harm avoidance, and increased vigilance for long-term surveillance for the sequelae of

chronic kidney damage among survivors. Importantly, we now recognize that AKI is not a bystander in critical illness. Patients no longer die with AKI, but from AKI. To improve the care and outcomes for sufferers of SA-AKI, clinicians need a robust appreciation for its epidemiology and current best-evidence strategies for prevention and treatment.

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