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.
Semin Nephrol 35:2-11
Keywords: acute kidney injury, sepsis, critical care nephrology, outcomes

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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Financial support: Supported in part by a grant from the National Institutes of Health (P50 DK096418 to R.B. and S.G.), and by a Canada Research Chair in Critical Care Nephrology and an Independent Investigator Award from Alberta Innovates–Health Solutions (S.B.).
Conflict of interest statement: none.
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0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2015.01.002

(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 ± 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

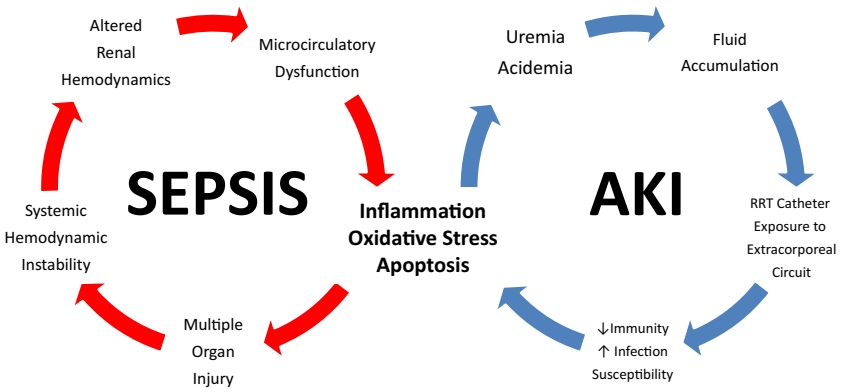

Figure 1. Sepsis and AKI pathophysiological interaction in SA-AKI. Reprinted with permission from Romanovsky et al.[92]

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-

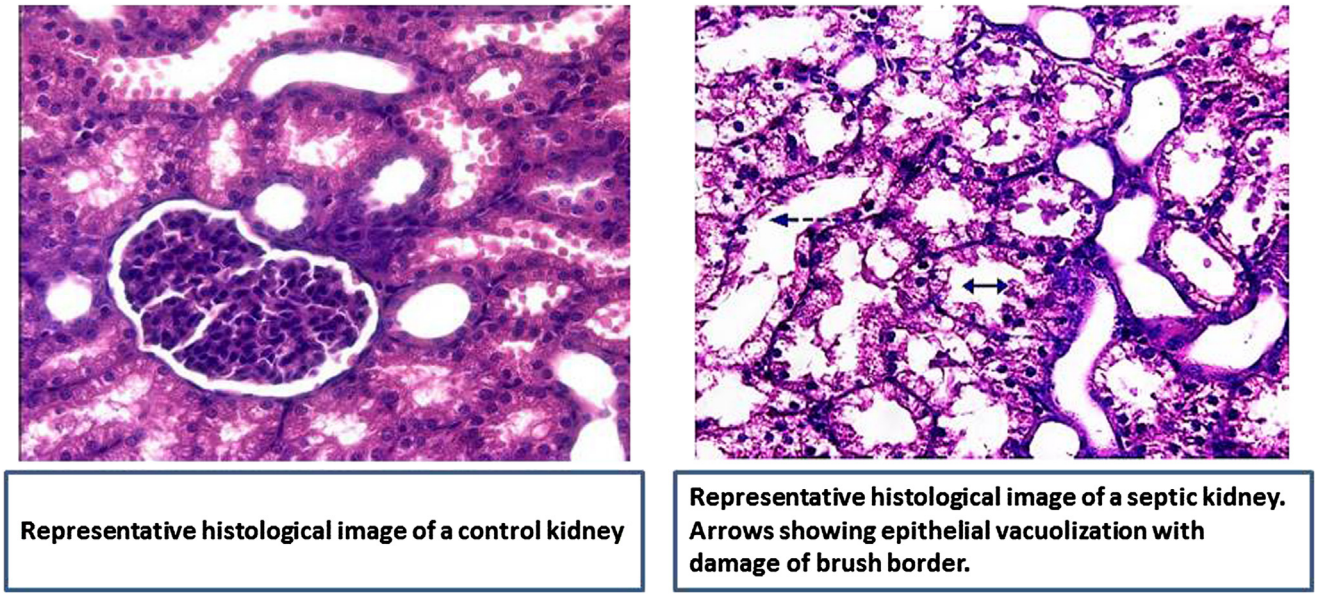

Figure 2. Porcine sepsis model does not show renal tubular necrosis. In a porcine model of fecal peritonitis, representative histopathologic cross-sections of renal tubules shows tubular vacuolization, a precursor of cellular apoptosis, but no evidence of necrosis. (A) Representative histologic image 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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Sepsis-Associated Acute Kidney Injury: Macrohemodynamic and Microhemodynamic Alterations in the Renal Circulation

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Summary: Traditionally, renal ischemia has been regarded as central to the pathogenesis of sepsis-associated acute kidney injury (SA-AKI). Accordingly, hemodynamic management of SA-AKI has emphasized restoration of renal perfusion, whereas, experimentally, ischemia reperfusion models have been emphasized. However, in human beings, SA-AKI usually is accompanied by hyperdynamic circulation. Moreover, clinical and experimental evidence now suggests the importance of inflammatory mechanisms in the development of AKI and microcirculatory dysfunction more than systemic alteration in renal perfusion. In this review, we examine systemic, regional, and microcirculatory hemodynamics in SA-AKI, and attempt to rationalize the hemodynamic management of this condition.
Semin Nephrol 35:64-74
Keywords: Acute kidney injury, sepsis, critical care, hemodynamic management, renal blood flow, microcirculation

Sepsis and septic shock remain the most important cause of acute kidney injury (AKI) in critically ill patients and septic-associated AKI (SA-AKI). They account for approximately 50% of cases of AKI in the ICU,[1] complicate between 15% and 20% of all ICU admissions with severe SA-AKI, and are responsible for triggering renal replacement therapy (RRT) in 2% to 3% of all ICU admission.[2] The mortality rate of critically ill patients with AKI severe enough to require RRT remains high at 40% to 55%, as shown in two recent major trials of acute RRT in the ICU.[3,4] In addition, large epidemiologic studies recently have linked AKI with the later development of chronic kidney disease, end-stage kidney disease, and late mortality.[5] These observations suggest that even a short episode of AKI may predispose the patient to long-term organ dysfunction, morbidity, and mortality.

Despite the importance of this condition, consensus, evidence-based treatment recommendations for SA-AKI remain limited to prompt and effective treatment of underlying infection, avoidance of secondary renal injury, and the monitoring and optimization of systemic hemodynamics.[6] Given the central role of hemodynamic management in the treatment of patients with or at risk of SA-AKI, an understanding of the relationship between systemic hemodynamics, renal blood flow (RBF), and glomerular filtration rate (GFR) is essential. In this review, we discuss the role of hemodynamic changes in the pathophysiology of septic AKI and mechanisms mediating reduction of GFR throughout the time course of AKI. With this knowledge, we then consider the physiological rationale for hemodynamic management of patients with SA-AKI.

PATHOPHYSIOLOGY OF SA-AKI

Sepsis and AKI are heterogeneous clinical syndromes and significant interindividual variation in pathogenesis is likely. A renal biopsy rarely is performed in patients with septic AKI and there is a dearth of human clinical histopathologic data on this condition. Unfortunately, many historic animal models on which we base our understanding of AKI have used ischemia-reperfusion or nephrotoxin-induced renal injury and may not relate directly to the pathogenesis of human SA-AKI.[7] These older models more closely reproduce the frank tubular necrosis observed as a result of massive crush injury and hypovolemia, or potent nephrotoxins that were more prevalent when AKI was first recognized as a clinical entity.[8,9] The pathology of AKI seen as a component of multi-organ dysfunction in contemporary patients appears less overt, involving inflammatory injury causing tubular cell dysfunction, associated with cell-cycle arrest, cellular de-differentiation, loss of intercellular tight

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Financial disclosure and conflict of interest statements: none.
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0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2015.01.007

junctions, loss of polarized transmembrane sodium channels, shedding of cytoskeletal debris into the tubular lumen, and cellular apotosis.[10–14] Such processes are accompanied by leukocytic infiltrates[13] and appear to have much in common with cellular injury occurring in other organs during septic shock.[15]

RBF and the Initiation of SA-AKI

Despite the differences in clinical context from the historic description of acute renal failure and acute tubular necrosis, SA-AKI, until recently, has been considered a predominantly ischemic phenomenon leading to renal tubular cell injury and death,[16] a paradigm largely translated from historic observations in animals and human beings with low cardiac output states (including massive hemorrhage, cardiogenic shock, or prolonged unresuscitated sepsis). The implication being that that restoration of adequate RBF should be the primary means of renal protection in critically ill patients. However, in human sepsis, a pattern of hyperdynamic septic shock predominates and other studies have found that the renal circulation participates in the systemic vasodilatation seen during severe sepsis/septic shock, so that global renal blood flow does not diminish, but SA-AKI still can develop. Furthermore, even if RBF reduction does occur, there is considerable evidence that subtotal renal ischemia alone is insufficient to initiate AKI. In a large animal model, occlusion of the renal arteries to reduce RBF to 10% of baseline resulted in only a transient decrease in GFR without sustained renal dysfunction after reperfusion.[17] Similarly, in patients surviving cardiac arrest without postresuscitation cardiogenic shock, AKI was uncommon, indicating that a significant period of periresuscitation warm renal ischemia may not be not sufficient to trigger clinical AKI in isolation.[18] These results are in harmony with historical accounts of ischemia-reperfusion in larger animal models in which protracted periods of complete ischemia were required to initiate fatal uremia: more than 1 hour in rabbits[8] and more than 3 hours in dogs.[19] Similarly, experimental shock by venesection in dogs progressively reduced renal plasma flow, but did not initiate irreversible ARF after resuscitation until renal perfusion was less than 1% of normal. Finally, massive hemorrhage (>50 mL/kg) was required to achieve such low renal blood flow.[19] Thus, RBF reduction alone appears insufficient to initiate AKI.

In fact, as noted earlier, experimental[20] and human[21] studies have suggested that RBF can be normal or increased in sepsis and during the development of AKI.[21,22] A comprehensive review of publications reporting renal perfusion in animal models of AKI found only a minority of the 160 reports identified reported both RBF and cardiac output. In these studies, if the model was associated with a hyperdynamic circulation (high cardiac output), RBF consistently was preserved or increased, and cardiac output was the only significant predictor of RBF in multivariate analysis.[23] Autoregulation of RBF has been shown to be impaired in critical illness[24] and during AKI,[25] so that RBF can vary with cardiac output, which may be normal, increased, or depressed, depending on the global hemodynamic context of a patient or the characteristics of the AKI model chosen. Thus, models using larger animals with hyperdynamic sepsis may be more relevant to human septic shock and the development of SA-AKI. These include models in which intravenous *Escherichia coli* is administered to sheep, in which AKI occurs despite significant increases in RBF, often by more than 100%.[22,26] Such renal hyperemia is associated with renal vasodilatation, and also oliguria and decreased creatinine clearance so that, in the short term, overt AKI occurs in the setting of renal hyperemia and renal vasodilatation.

In the sheep model, renal vasodilatation may be caused by endothelial and neural nitric oxide synthase–derived nitric oxide, however, nitric oxide synthase blockade did not restore renal function.[27] Furthermore, in this model, creatinine clearance decreased even with milder hyperdynamic sepsis associated with increased cardiac output, but not systemic hypotension.[28] These observations suggest that hemodynamic and inflammatory changes within the kidney, rather than overall renal vascular resistance, may account for any decreases observed in GFR. Such changes may include an imbalance between preglomerular and postglomerular resistance (affecting glomerular ultrafiltration pressure) and/or alterations in the renal microcirculation (affecting tubular and glomerular function). A final possibility is that, even though there is preserved or increased global RBF in septic AKI, internal redistribution of blood flow favoring the cortex may occur, so that ischemia at the corticomedullary junction then would mediate tubular injury and SA-AKI. However, no evidence exists to confirm this mechanism in hyperdynamic sepsis using technology that allows continued measurement of medullary and cortical blood flow over time. In an investigation using Doppler flowmetry to monitor medullary and cortical flow in septic sheep,[29] both flows remained unchanged and the administration of vasopressor therapy (noradrenaline) induced a significant increase in both.

Thus, it appears that, at least in the early phases of severe sepsis, the loss of GFR is mediated by mechanisms other than tubular ischemic injury, and that tubular injury, if and when it occurs, may not be caused directly by global or regional changes in blood flow.

Inflammatory Versus Ischemic Mechanisms in SA-AKI

Even in smaller-animal models of experimental sepsis or endotoxemia[30] in which global RBF does decrease,[31] the evidence that reduction in global renal oxygen delivery is the triggering event in SA-AKI is weak. In rodent models, increased renal capillary permeability has been shown to occur before decreases in RBF,[32] and any changes in RBF have been accompanied by altered cortical microcirculatory hypoperfusion,[31,33] peritubular capillary leakage, and reactive nitrogen species generation.[33] This suggests that the triggering event in these models of SA-AKI may be local inflammation and microvascular disturbance rather than global renal ischemia. The role of decreased global renal oxygen delivery in the pathogenesis of SA-AKI is questioned further by studies examining oxygen transport and mitochondrial function in SA-AKI models. In a porcine fecal peritonitis model, tissue hypoxia did not appear to be a major pathophysiological factor during early and established SA-AKI because mitochondrial respiration remained normal, despite shock and renal hypoperfusion.[34] Similarly, in a rat endotoxemia model, increased oxygen extraction maintained the gradient between microvascular Po_2 and tissue oxygen tension in both the cortex and outer medulla, despite decreased renal perfusion, oxygen delivery, and urine output.[35] Finally, in severe experimental hypotensive sepsis in sheep in which, after an initial increase, RBF then decreased (presumably owing to profound systemic vasodilation and myocardial depression), renal adenosine triphosphate levels, as measured by magnetic resonance imaging spectroscopy, remained unchanged.[36]

In fact, even in ischemia-reperfusion models, the role of ongoing renal ischemia in the progression of AKI is unclear. For instance, in a pig model of aortic cross-clamping, renal reperfusion RBF initially was restored and only then decreased progressively, despite normal systemic hemodynamics,[37] suggesting that intrarenal factors including endothelial injury, microvascular thrombosis, and inflammation were causing microcirculatory hypoperfusion and increasing renal vascular resistance.[38]

Collectively, this evidence suggests that inflammatory responses and inflammatory alterations in the microcirculation are responsible for the progression and maintenance of AKI whether or not this is initiated by ischemia. In SA-AKI, systemic inflammatory responses are likely to be the dominant factor. Proposed mechanisms include inflammatory responses that may be triggered by ligation of Toll-like receptors, by pathogen- and damage-associated molecular patterns (Toll-like receptor-4 has been implicated in animal models of SA-AKI[39]), and damage pathways involving the generation of reactive oxygen species[32,40] and Fas/Fas ligand interactions.[41]

RBF in Established AKI

Although a reduction in RBF and renal oxygen delivery is neither necessary nor sufficient for the initiation of sustained SA-AKI, a large number of human clinical studies have established that all forms of AKI are associated with a reduction in RBF,[25,42] in many cases despite normal systemic blood pressure and cardiac output.[42] In particular, established AKI appears to be associated with a reduction in the renal fraction of cardiac output. This suggests that intrarenal factors are specifically increasing renal vascular resistance in response to AKI, resulting in decreased RBF and renal fraction once AKI has developed. Furthermore, because GFR reductions are disproportionately greater than RBF reductions in human AKI studies in which both were measured,[43] renal vasoconstriction preferentially may be preglomerular, causing a disproportionate decrease in glomerular capillary hydrostatic pressure.

Again, inflammatory mechanisms may mediate changes in renal vascular resistance during AKI indirectly or directly, in a porcine sepsis model a progressive increase in renal vascular resistance occurred 18 to 22 hours after induction of sepsis, but only in animals developing AKI. However, these changes were preceded by significant increases in plasma proinflammatory cytokines in affected animals,[44] suggesting that specific alterations in the renal circulation occur in SA-AKI in association with greater systemic and local inflammation.

MECHANISMS OF REDUCTION IN GLOMERULAR FILTRATION IN SA-AKI

Despite the paucity of histopathologic findings in SA-AKI and the predominant tubular localization of any cellular injury that does occur, the defining clinical feature of AKI remains a reduction in glomerular filtration, resulting in biochemical abnormalities as solutes accumulate in the plasma. To understand the rationale for hemodynamic interventions in AKI, we need to consider the mechanisms by which GFR reductions may occur.

Glomerular Filtration and Systemic Hemodynamic Alterations

The rate of glomerular ultrafiltration is proportional to the pressure gradient between the glomerular capillary and the tubular space, modified by the permeability of the glomerular capillary wall, and opposed by the build-up in the colloid osmotic gradient as selective ultrafiltration occurs along the length of the glomerular capillaries (Fig. 1A). Importantly, the normal mean pressure gradient driving ultrafiltration is only approximately 10 mm Hg, demanding close autoregulation of

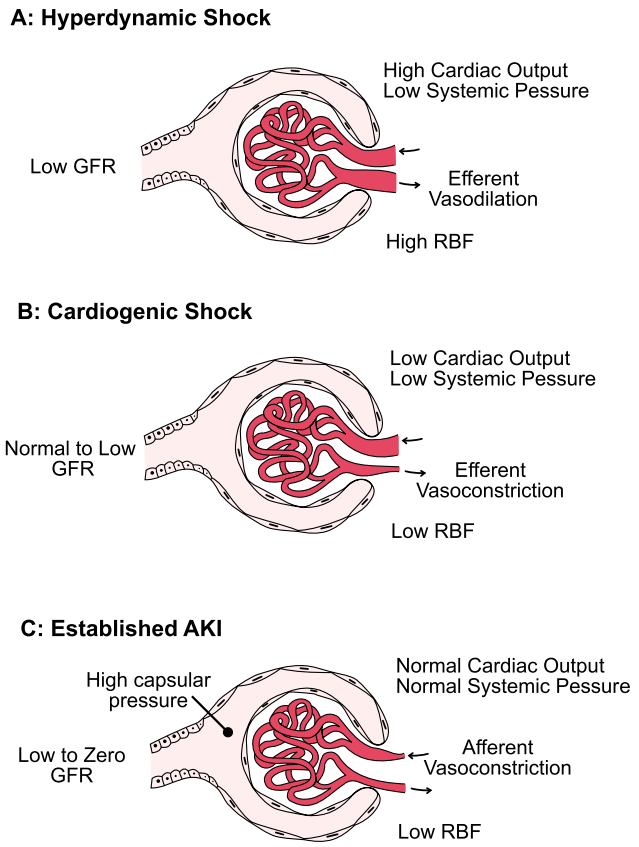

Figure 1. Glomerular and systemic hemodynamic abnormalities in disease states. (A) Hyperdynamic septic shock: high RBF, low pGC, and low GFR. (B) Low cardiac output states: low RBF, relatively maintained pGC, and normal to low GFR. (C) Established AKI: low RBF, low pGC, high capsular pressure, and low/no GFR.

glomerular capillary pressure (pGC) by modification of the relative resistances in the afferent and efferent glomerular arterioles to maintain GFR.

Vasodilatation of the afferent arteriole transmits systemic arterial pressure more directly to the glomerulus and promotes ultrafiltration, whereas vasoconstriction of the efferent arteriole maintains pressure in the glomerulus by increasing the proportion of total renal vascular resistance that is postglomerular. In addition, ultrafiltration leads to concentration of the remaining plasma, increasing the osmotic pressure resisting ultrafiltration. Thus, for any given pGC, the GFR will be greater with higher overall renal plasma flow as less relative concentration occurs per unit of ultrafiltration. Moreover, afferent vasodilation will favor glomerular filtration as long as systemic perfusion pressure is sufficient to generate a pGC greater than the critical level of approximately 50 mm Hg, whereas afferent vasoconstriction effectively abolishes filtration by a reduction of both the pGC and renal plasma roles (Fig. 2A).

Conversely, efferent constriction will increase pGC by restricting outflow; however, any resultant increase in GFR is limited by the overall reduction in renal plasma flow that accelerates the increase in osmotic pressure with ultrafiltration. In contrast, efferent vasodilation will result in a low-pressure–high-flow renal circulation in which, despite high renal plasma flow, pGC may be too low to drive effective ultrafiltration (Fig. 2B).

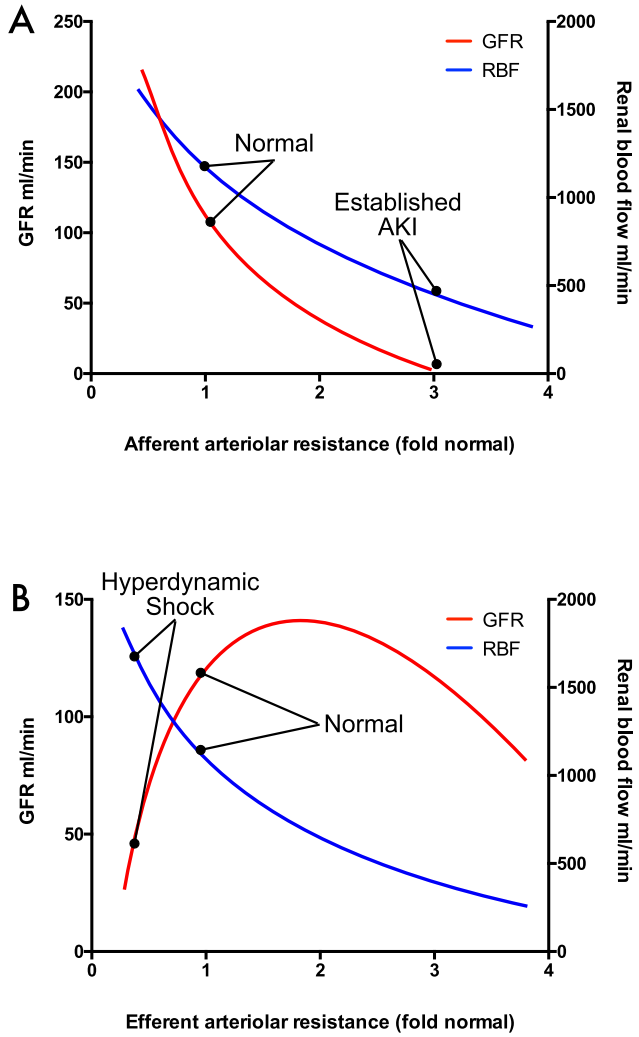

Figure 2. Variations in RBF and GFR with isolated alteration in (A) afferent or (B) efferent resistance. (A) Afferent arteriole constriction (which may occur in sustained AKI) reduces both RBF and hydrostatic pGC in parallel (because renal vascular resistance is increased proximal to the glomerulus), as a result GFR decreases markedly with increasing afferent resistance. Conversely, afferent vasodilation will tend to increase pGC (by transmitting systemic blood pressure more directly to the glomerular circulation) and increase RBF, resulting in a larger increase in GFR. (B) Efferent vasodilation (as may occur in hyperdynamic sepsis) increases renal blood flow by reducing overall renal vascular resistance, but at the same time tends to reduce pGC owing to reduced distal resistance, creating high-flow–low-pressure glomerular circulation. In the context of systemic hypotension this can result in significant reduction in GFR despite increased RBF. Conversely, afferent constriction will increase pGC by restricting glomerular outflow, even though overall RBF is reduced, the larger increase in pGC will increase GFR until reduction in RBF becomes limiting as a result of the effect of increased oncotic pressure during ultrafiltration.

In the context of a low cardiac output state and systemic hypotension, myogenic reflex vasodilatation of the afferent arteriole in response to systemic hypotension and preferential vasoconstriction of the efferent arteriole mediated by activation of the renin angiotensin aldosterone system and renal sympathetic innervation will act to maintain GFR and RBF until systemic perfusion pressure decreases below a critical value and filtration ceases (Fig. 1B). In contrast, in hyperdynamic septic shock, cardiac output is increased in the context of systemic vasodilation and hypotension. In these circumstances, systemic vasodilation will affect the kidney. Because baseline efferent tone is higher than afferent tone, this causes preferential efferent vasodilation and the development of a high-flow–low-pressure renal circulation in which GFR becomes uncoupled from the increase in RBF (Fig. 1C). It is unknown how long RBF may remain increased if hyperdynamic sepsis is sustained, however, a longer-term model (48 hours) of septic AKI achieved by the continuous intravenous infusion of live *E coli* at a dose carrying limited lethality[22] found that cardiac output increased three-fold over time and that RBF increased at almost exactly the same rate; both were associated with a progressive decrease in urinary output to near anuria and a reduction in creatinine clearance by 80%. The serum creatinine level increased four-fold. During recovery from this AKI model, the same changes seen were seen as during sepsis, but in reverse with recovery of GFR and RBF.[26]

Thus, both a hypodynamic circulation (Fig. 1A) and a hyperdynamic circulation (Fig. 1B) can result in significant reductions in GFR and biochemical renal dysfunction; however, at least in theory, these derangements should be fully reversible with correction of the systemic hemodynamic abnormality. However, in most clinical situations, initial hemodynamic abnormalities are accompanied or preceded by systemic or renal inflammatory responses and/or nephrotoxin exposure leading to tubular injury, thus renal dysfunction may persist even after resolution of hemodynamic abnormalities.

GFR Alterations in Persistent AKI

The mechanisms by which GFR is reduced in persistent AKI are distinctly different from the early GFR changes driven by systemic hyperdynamic or hypodynamic states. Loss of renal clearance must involve either failure of ultrafiltration or subsequent reabsorption of the ultrafiltrate. A number of mechanisms can link observed loss of glomerular excretory function with the predominantly tubular kidney injury seen in SA-AKI in particular: pathologic activation of tubuloglomerular feedback, tubular obstruction, tubular back-leak, tubular stasis, renal edema, and altered glomerular permeability (Fig. 3).

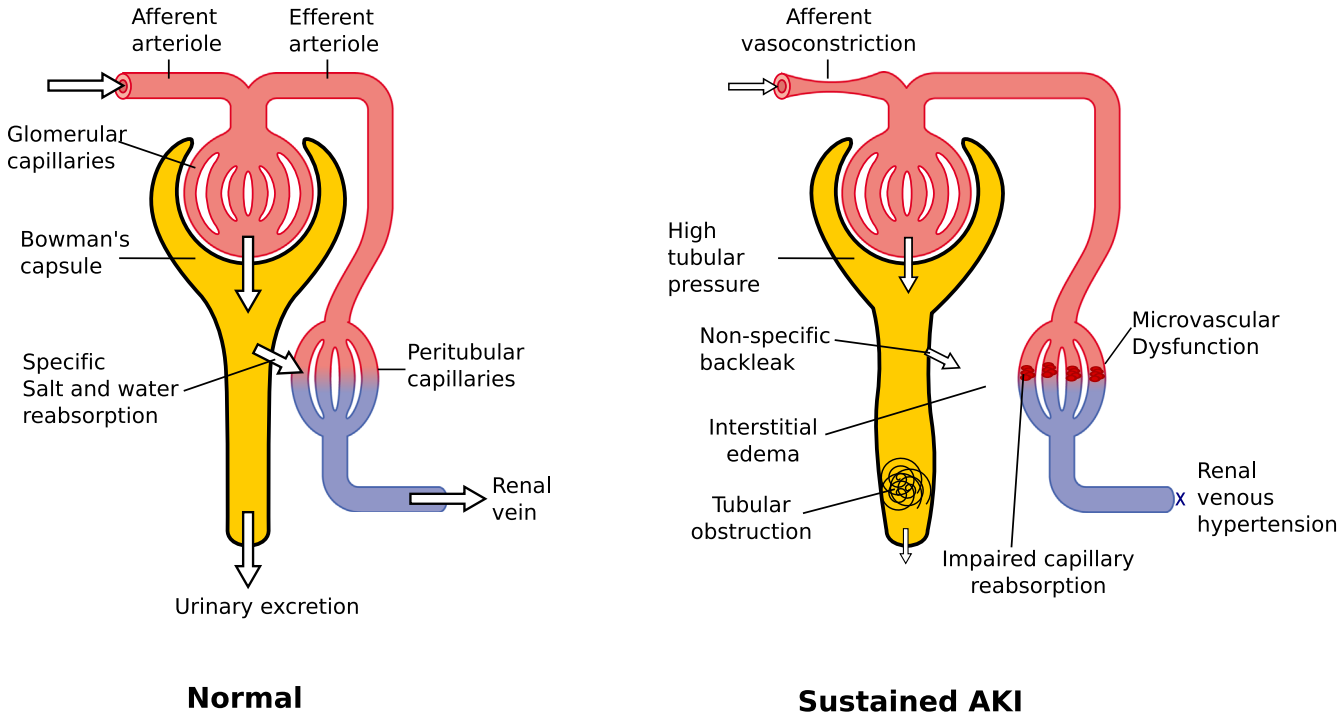

Figure 3. Mechanisms of filtration failure in established AKI. Afferent vasoconstriction secondary to TGF activation causes low glomerular hydrostatic pressure whereas tubular and interstitial pressure is increased secondary to inflammatory responses, microvascular dysfunction, tubular obstruction, and failure to resorb filtered salt and water. Increased venous pressure contributes both to reduced renal perfusion and increased renal interstitial pressure.

The tubuloglomerular feed-back (TGF) mechanism[45] is activated by increased chloride delivery to the distal nephron and causes afferent arteriolar constriction. Normally TGF is activated in the context of high glomerular perfusion pressure causing hyperfiltration, when activation of the TGF response appropriately limits hyper-filtration. During AKI, however activation of TGF can occur in the context of tubular dysfunction as in the chloride load delivered to the macula densa is elevated in the context of impaired tubular reabsorption, not increased filtration. In this context the TGF-mediated afferent vasoconstriction can cause very marked reduction in GFR, particularly in combination with systemic hypotension or raised intra-capsular pressure. Although TGF responses limiting GFR in the context of tubular injury could be regarded as pathologic, it has been speculated that they might be protective by limiting excessive volume loss that might occur if the GFR was preserved in the context of impaired tubular reabsorption and limiting renal oxygen consumption in a time of stress by reducing filtered sodium.

Obstruction of the tubular lumen with cellular debris could increase tubular pressure proximally, resulting in a decreased filtration gradient, however, dilatation has not been observed in tubules obstructed by casts and these casts are flushed easily from tubules, arguing against this mechanism.[9]

Tubular cell dysfunction, loss of tight junctions, and loss of tubular integrity leading to unselective leakage of ultrafiltrate could cause loss of effective GFR in two ways: first, by causing total reabsorption of the filtrate (so-called back-leak), eliminating the generation of urine despite ultrafiltration, and, second, by causing renal edema, increasing renal intracapsular pressure and opposing filtration. The evidence for back-leak in animal models is mixed. First described in the 1920s, in microscopic observations of single nephrons in the frog, it seems to play a role in nephrotoxin-induced renal failure. In addition, the persistence of ultrafiltration in experimental cases of complete outflow tract obstruction[46] implies that some degree of back-leak must be occurring in this situation. However, in human AKI it appears that suppression of glomerular filtration is by far the most important mechanism mediating reduction in renal clearance.[47,48] Conversely, sustained oliguric AKI (>7 d) has been associated with persistent tubular dilatation and a persistent reduction in the glomerular pressure gradient for ultrafiltration, perhaps partially owing to increased tubule pressure. Notably, tubular capillary uptake of fluid-resorbed tubular lumen is mediated passively by oncotic pressure, so that a high filtration fraction will mediate increased uptake of tubular fluid by increased plasma osmotic pressure, allowing tubule-glomerular balance.[49] In AKI, reduced filtration and capillary inflammation might disrupt this process, causing accumulation of fluid in the interstitium and the tubular lumen, increasing pressure opposing ultrafiltration.

Evidence in support of a role for increased renal tissue pressure in the maintenance of AKI can be found from measurements of pressure made in an animal ischemia-reperfusion model of AKI. In this model, the development of renal dysfunction was associated with increased renal subcapsular pressure in proportion to the duration of the ischemic insult, and relief of increased pressure by renal decapsulation was associated with late recovery of renal function.[50]

A final mechanism that could mediate reduction in GFR in SA-AKI is an alteration in glomerular permeability directly limiting filtration as a result of sepsis-induced injury to glomerular epithelium and/or endothelium. Some evidence exists for this process in animal models,[51–53] but the significance of this mechanism in human SA-AKI remains unexplored.

Summary of Mechanisms in Septic AKI

Overall, it seems likely that, during the initial stages of septic shock, GFR is reduced as a combination of preferential efferent renal vasodilation and systemic hypotension. RBF is maintained or increased (although it may decrease as a fraction of cardiac output); however, glomerular capillary hydrostatic pressure is insufficient to permit effective filtration, particularly in the context of secondary risk factors. Such factors include impaired renal autoregulation and a fixed increase in renal afferent resistance, as seen in chronic hypertension and chronic kidney disease or exposure to agents that may cause afferent constriction or worsen efferent vasodilation (nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, radiologic contrast, or angiotensin-converting enzyme inhibitors).

These hemodynamic alterations may be fully correctable with vasopressor therapy.

Inflammatory tubular and microvascular injury often accompanies severe systemic sepsis, potentially resulting in progressive afferent constriction (as a result of TGF), and increased tubular pressure, resulting in sustained loss of filtration. This phenomenon may be less sensitive to hemodynamic therapy and may persist until intact functional tubular epithelium has regenerated and increased renal interstitial pressure has resolved. Thus, as the initial hemodynamics evolve, sepsis-related injury to the kidney via a host of other mechanisms related to microvascular dysfunction and mitochondrial and tubular damage can become the dominant form of kidney injury if the sepsis/inflammatory insult persists.

HEMODYNAMIC MANAGEMENT FOR SA-AKI

The choice of hemodynamic management in patients with or at risk of SA-AKI depends on the global clinical and hemodynamic status and stage in the natural history of AKI (potential for rapid reversibility). Many hemodynamically active agents have been examined in the context of SA-AKI. (Table 1)

Fluids

Intravenous fluids remain a cornerstone of the hemodynamic management of septic shock. Although there is a clear rationale for the treatment of an acute decrease in circulating volume as a result of capillary leak and dilation of central venous reservoirs, the extent and duration of hemodynamic responses to fluid therapy in systemic inflammatory states is attenuated and fluid overload often is an inevitable consequence of ongoing fluid therapy. Importantly, fluid therapy will be incapable of effectively reversing vasodilatory shock.

The limited effects of fluid therapy on renal perfusion have been illustrated in a number of animal studies. In healthy sheep, administration of crystalloid or colloid solution effectively increased cardiac output, renal blood flow, and systemic blood pressure; however, this effect was transient and renal oxygen delivery was not augmented because hemodilution offset any increase in RBF.[54] In a rat model of hemorrhagic shock, fluid therapy sufficient to restore systemic blood pressure failed to restore measures of renal tissue oxygenation.[55] Similarly, in an endotoxemia rat model of septic shock, immediate fluid resuscitation reduced renal inflammation, but did not prevent reduction in renal microvascular oxygenation.[31] Furthermore, a substantial body of evidence suggests adverse outcomes may be associated with the development of fluid overload in septic shock and in particular in the context of AKI.[56] A variety of direct and indirect mechanisms may explain this association.

Compared with other hemodynamic variables, increased central venous pressure has been shown to better predict worsening renal dysfunction in acute decompensated cardiac failure[57] and in critically ill patients with septic shock,[58] suggesting a potential role for venous congestion in the pathogenesis of AKI in these conditions. This hypothesis is supported by a long history of physiological data. More than 80 years ago, venous occlusion was shown to reduce renal blood flow, urine flow, and solute excretion to the same or greater extent than the same degree of arterial occlusion in isolated dog kidneys.[59] Similar results were reported in 2012 in a murine ischemia-reperfusion model in which selective clamping of the renal vein was shown to mediate more severe renal injury and renal dysfunction than a similar duration of arterial occlusion.[60] Significantly, increases in venous pressure have been shown to lead directly to increased renal interstitial and peritubular pressure in the rat,[61] suggesting that venous congestion may limit glomerular filtration as well as impair renal macrovascular and microvascular perfusion. In this fashion, fluid overload and venous congestion could potentiate the increased interstitial pressure seen in sustained AKI in animal models.[50]

In addition to any volume or congestion effects, fluid composition may have adverse effects on renal function. Although theoretically capable of more sustained intravascular expansion, hydroxyethyl starch preparations are potentially nephrotoxic and are not recommended in patients with or at risk of AKI.[62–65] However, hyperchloremic crystalloid solutions such as 0.9% saline also may have adverse, direct hemodynamic effects on the kidney. In human beings, administration of unbuffered isotonic saline solutions has been shown to cause renal vasoconstriction.[66] Potentially, this might occur by activation of TGF

Table 1. Reported or Likely Effects of Fluids and Vasopressors on Hemodynamic Aspects Relevant to Septic AKI

Key Variable	Fluids	Vasopressors
Mean blood pressure	Variably Increased +	Increased +++
Cardiac output	Variably Increased ++	Increased +
Afferent arteriolar tone	No direct effect	Variable effect
Efferent arteriolar tone	No direct effect	Increased
Intracapsular pressure	Increased	Unchanged
Venous congestion	Increased	Unchanged
Glomerular oncotic pressure	Decreased with crystalloids	Unchanged
Chloride load to macula densa/TGF activation	Increased	Unchanged
Delivery	Boluses	Continuous infusion
Duration of beneficial effects	Hours only requiring repeated boluses	During infusion
Duration of adverse effects	Cumulative as fluid overload accumulates	During infusion

mechanisms and afferent vasoconstriction. Observationally, use of buffered solutions has been associated with a lower incidence of AKI,[67,68] suggesting that this effect may be clinically significant.

Vasopressors

In comparison with fluid therapy, vasopressors directly target pathophysiological vasodilation in hyperdynamic septic shock; however, historically, the application of vasopressor therapy was tempered by concerns that excessive vasoconstriction might limit renal blood flow. However, in dog models, noradrenaline has been shown to increase renal blood flow by increasing renal perfusion pressure and decreasing renal sympathetic tone,[69] and to reverse endotoxemia-induced hypotension without impairing renal perfusion.[70] Similarly, in sheep models of gram-negative sepsis, administration of noradrenaline[29] or phenylephrine[71] (a pure vasoconstrictor) have been shown to augment renal function and promote diuresis. In human beings, use of vasopressors to increase mean blood pressure from 60 to 75 mm Hg has been shown to increase RBF and GFR in patients with AKI after cardiac surgery.[72] Phenylephrine, a pure vasoconstrictor, has a similar effect in an animal model of AKI, suggesting renal perfusion pressure is important in determining RBF in AKI.

However, use of vasopressors to restore blood pressure may not affect the inflammatory pathogenesis of SA-AKI[39] and response to vasopressor therapy may depend on the time point in the disease process, severity of renal insult, and the patient's premorbid condition. Recently, blood pressure targets in septic shock were examined in a large randomized trial of 776 critically ill patients requiring vasopressor infusions for septic shock, comparing a target mean arterial pressure of 65 to 70 mm Hg against a target of 80 to 85 mm Hg. Although no difference in mortality or renal dysfunction was seen in the overall cohort, in a prespecified group of patients with a prior history of hypertension, a high blood pressure target was associated with a lower incidence of renal dysfunction and need for RRT. This suggests that higher renal perfusion pressure may be required to prevent SA-AKI in patients with increased baseline renal vascular resistance.

The effects of vasopressors, therefore, are likely to benefit renal function in sepsis by favorably modifying glomerular hemodynamics and reversing the high-flow–low-pressure circulatory abnormality. This is likely to occur both by increasing renal perfusion pressure and by a greater increase in efferent arteriolar tone. Reversal of efferent vasodilation may be particularly important in restoring GFR and urine output. In controlled animal studies comparing intravenous infusion of the preferential efferent vasoconstrictor angiotensin II with placebo in the setting of experimental SA-AKI,[73] urinary output increased dramatically, as did creatinine clearance, even as renal blood flow decreased from supraphysiological levels.

Other studies have supported the view that preferential efferent arteriolar vasoconstriction might improve GFR. For example, arginine vasopressin (AVP) causes calcium release from intracellular stores, which in turn contributes to the contractile response of both afferent and efferent arterioles. However, such response is more prominent in the efferent arteriole[74] and appears to lead to increases in pGC. In support of these observations, in models of SA-AKI, AVP has been shown to increase creatinine clearance significantly with no change in RBF.[75] These observations are supported by clinical data from the Vasopressin and Septic Shock Trial investigators,[76] who, in a post hoc analysis of a multicenter, double-blind, randomized, controlled trial of AVP in septic shock, showed that, in patients enrolled with early, but not established, renal dysfunction (RIFLE-Risk AKI), AVP infusion was associated with a decreased progression to the most severe category of AKI and a lower risk of use of RRT.[77] These findings from the Vasopressin and Septic Shock Trial are largely consistent with large mammal preclinical studies of SA-AKI.[75,78]

CONCLUSIONS

In adult human beings, early septic shock is associated more commonly with hyperdynamic circulation and is likely to be associated with high-flow–low-pressure renal circulation. Timely reversal of these circulatory abnormalities with vasoconstrictors may reverse early hemodynamically mediated renal dysfunction, and higher blood pressure targets may be justified in patients with pre-existing hypertension. The optimal choice of vasopressor has not been established, however, agents such as AVP may have specific renal benefit and a multicenter randomized trial examining renal outcomes with AVP use in early septic shock is ongoing (VAsopressin vs Noradrenaline as Initial therapy in Septic sHock: ISRCTN20769191). Conversely, excessive fluid loading beyond restoration of acute hypovolemia may worsen renal function by causing venous congestion and increased interstitial pressure. However, the pathogenesis of tubular injury in SA-AKI is likely to be related more to inflammatory responses than to direct effects of global hemodynamic alterations, and, once AKI is established, RBF and GFR may be limited by intrarenal factors and respond little to manipulation of systemic hemodynamics. Thus, in contrast to early or developing AKI, in established SA-AKI, hemodynamic targets might reasonably be conservative because achieving higher

blood pressures (>60-65 mm Hg) with vasopressors has not been associated with improved survival. In all cases and at all times, the development of fluid overload has been associated consistently with adverse outcomes and should be avoided.

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Clinical Approach to the Patient With AKI and Sepsis

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Summary: Sepsis and acute kidney injury (AKI) frequently are combined in critical care patients. They both are associated independently with increased mortality and morbidity. AKI may precede, coincide with, or follow a sepsis diagnosis. Risk factors for sepsis followed by AKI differ from those associated with AKI preceding or coinciding with sepsis, and the pathophysiologic mechanisms may be different. In this article, we review the available clinical, laboratory, and imaging tools available for the recognition of septic AKI. Early identification of high-risk patients and targeted preventive and therapeutic measures are key to reducing the mortality and morbidity of the complex syndrome of septic AKI.
Semin Nephrol 35:12-22
Keywords: sepsis, AKI, renal injury, management

Acute kidney injury (AKI) frequently is associated with sepsis. Its incidence varies from 11% to 42%,[1,2] and may be as high as 67% in a septic surgical population.[3] Sepsis is the most common cause of AKI in critical care patients, accounting for 50% of cases in the intensive care unit (ICU).[4] AKI incidence rate and severity correlate with the severity of the underlying sepsis.[5] Septic AKI is a hallmark of severe sepsis and septic shock and is associated with worse outcomes including prolonged hospital length of stay, fewer ventilator-free days, and increased mortality when compared with patients with nonseptic AKI.[2,3] It appears that septic AKI is different than nonseptic AKI with respect to the underlying contributing factors, and severity of injury and outcomes. Septic patients develop more severe AKI than nonseptic patients and even patients with nonsevere infections (eg, pneumonia) have a significantly higher incidence of AKI.[2,6] Pathophysiological mechanisms that are discussed in detail elsewhere in this journal. Several factors have been implicated in the pathogenesis of septic AKI. Hemodynamic changes in the macrocirculation (ie, vasodilatation and increased cardiac output), and systemic and renal microcirculation contribute to renal hyperemia coupled with inefficient cellular oxygen extraction. The renal medulla is particularly sensitive to these hemodynamic perturbations and resultant hypoxemia because it already is functioning at a lower partial pressure of arterial oxygen level, especially in the nephrons of the corticomedullary junction. Sepsis also is associated with systemic inflammation and endothelial dysfunction, which also have been shown to contribute to renal injury and enhance microcirculation perturbations.[7,8] The stress response is altered in sepsis; the earliest phase is characterized by a short-lived hyporesponsiveness, which is followed by a dramatic phase of hyper-responsiveness. In the hyper-responsive phase, both proinflammatory and anti-inflammatory cytokines are released into the systemic circulation, and endothelial exposure of local adhesion receptors leads to platelet aggregation with microthrombi formation and enhanced leukocyte recruitment. This excessive immune response with deregulation between the proinflammatory and anti-inflammatory mediators contributes to further downstream or distant organ damage such as AKI. The later phase of sepsis is characterized by hypofunctionality of the immune system, which may last from several days to weeks, and increases susceptibility to new or recurrent infections. The complex interplay of various factors during the course of sepsis makes it difficult to identify the exact mechanism and pathways in septic AKI (Fig. 1).

Although there is a significant body of literature supporting an important role of inflammation in the pathogenesis of septic AKI, the use (to date) of interventions that reduce the inflammatory state seen in sepsis have not been successful in reducing AKI risk. In a prospective cohort study by Murugan et al,[9] the use of statins (which have a pleiotropic anti-inflammatory effect) in patients presenting with pneumonia was associated with a reduction in the risk of AKI that did not remain statistically significant after adjusting for confounders (odds ratio, 0.72; $P = .09$).

SEPSIS AND AKI: TIMING AND RISK FACTORS

AKI in the setting of sepsis can be considered in three different domains: sepsis preceding AKI, concurrent

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Financial disclosure and conflict of interest statements: none.
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0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2015.01.003

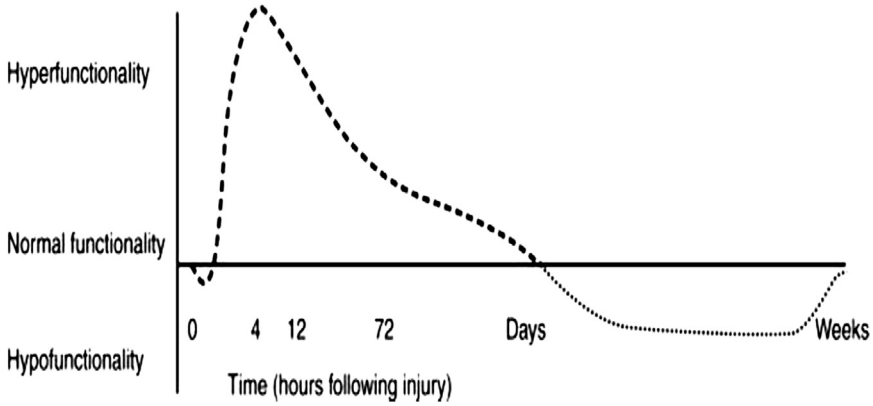

Figure 1. Immune hyporesponsiveness and hyper-responsiveness phases in sepsis.

presentation of sepsis, and AKI and sepsis after AKI (Fig. 2).

It generally is well accepted that sepsis greatly increases the risk of AKI, but there is growing evidence that AKI itself increases the risk of sepsis. In a post hoc analysis of the prospective multicenter PICARD (Program to Improve Care in Acute Renal Disease) study with AKI patients, 40% of the patients developed sepsis after they developed AKI (median, 5 d), compared with 28% in whom sepsis preceded AKI. The mortality rate was similar between groups, but when they were compared with a group of AKI patients without sepsis, both groups had higher mortality rates, risk of requiring dialysis, and a longer hospital length of stay. Significant predictors of sepsis in AKI patients identified in this study were fluid accumulation, oliguria, severity of illness score, nonsurgical procedures, and dialysis.[10] Different mechanisms may explain the increased risk of sepsis in AKI patients. Uremia appears to affect distant organ function. For example, it is associated with immune system dysfunction, impaired leukocyte trafficking, cytokine regulation, and vascular permeability.[11] Immunoparalysis has been described in chronic kidney disease and especially in the end-stage renal disease population with increased risks of pneumonia and sepsis.[12] It now increasingly is believed that similar changes occur with AKI. Critical care patients with AKI have impaired monocyte cytokine production associated with high levels of plasma cytokines.[13] Impaired local protective barrier mechanisms associated with the fluid overload often seen with AKI also may contribute to increasing sepsis risk (eg, edema, third spacing or volume sequestration, skin or gastrointestinal barrier breakdown with bacterial translocation, and edema with poor wound healing, ultimately leading to infection). Patients with AKI requiring dialysis also are at increased risk of bacteremia and endocarditis through central venous catheter insertion or peritoneal dialysis catheter placement. AKI increases length of stay in the hospital, which itself is a well-known risk factor for nosocomial infections. AKI treatment also may increase the risk of infection or sepsis by mechanisms beyond simple underdosing of antimicrobial drugs (by either inadequate supplemental dosing to correct for drug removal by renal replacement therapy (RRT), or failure to augment dose during AKI recovery). A rapid reduction through dialysis of neutrophil gelatinase-associated lipocalin (NGAL), a known antibacterial factor of natural immunity, perhaps may increase the risk of subsequent infection or sepsis.[14] Erythropoietin, also reduced with AKI, similarly may have an immunomodulatory effect.

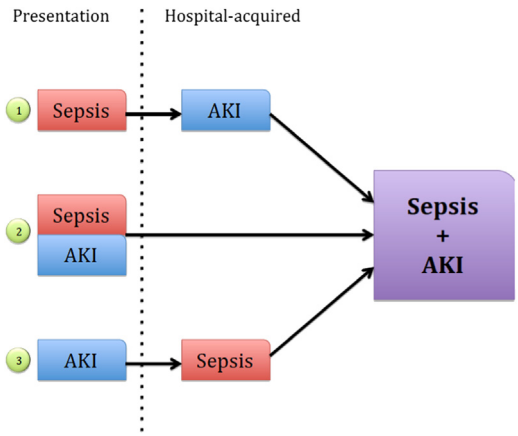

Figure 2. Three models of sepsis and AKI classified by sequence of injury. (1) Patient presents with sepsis and later develops AKI (late septic AKI). (2) Patient presents with simultaneous AKI and sepsis (early septic AKI). (3) Patient presents with AKI and later develops sepsis.

The risk of developing AKI after sepsis is higher in older male patients, and those with increased severity of illness, lower urinary output, higher central venous filling pressures, vasopressor requirements, and preexisting treatment with angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers.[1,15–17] Serum creatinine level at presentation and a pH of less than 7.3 also have been identified as predictive of AKI in septic patients.[1] A recent retrospective study analyzing

more than 4,000 septic patients found that the presence of septic AKI varied significantly based on source of infection, with nonpulmonary infections having higher risks for AKI development. After multivariable analysis, no specific type of pathogen was associated with increased septic AKI risk compared with others.[18] On the other hand, another study did identify a higher number of positive blood cultures, especially gram-negative bacilli and fungi, in septic AKI patients compared with septic patients who did not develop AKI.[17] In addition, several clinical characteristics differ between patients with septic AKI and those with nonseptic AKI. Septic AKI patients tend to be older, have more comorbid disease, are more likely to be admitted to the medical ICU, have higher severity of underlying illness scores, and have greater abnormalities in vital signs, markers of inflammation, and blood chemistry.[2]

Considering all of these arguments, it must be emphasized that not only is sepsis a risk factor for AKI, but AKI itself appears to be a risk factor for sepsis. In some situations, the sepsis clearly precedes the kidney injury, but other cases might not be so clear, leading one to wonder, "is the kidney a victim or the cause of the sepsis?" AKI therefore may be a cause and a consequence of sepsis. The fact that mortality rates associated with early versus late development of sepsis in AKI patients do not differ indicates that although the latter has been under-recognized in the past, it carries significant consequences.

RECOGNITION

Clinical manifestations of sepsis with AKI depend on many factors. AKI may precede or be followed by sepsis. They may also be simultaneous at presentation. These variations influence patient's initial clinical features. One therefore must keep sepsis features in mind when evaluating a patient with AKI and conversely evaluate for AKI when a patient presents with sepsis.

Signs and symptoms of sepsis vary not only with organ involvement, but also from one individual to another owing to patient- and disease-specific characteristics and susceptibilities. Signs of sepsis reflect the phase of the disease and range from features limited to the primary organ (eg, pneumonia) to severe multiorgan dysfunction syndrome and septic shock. Caregivers therefore must be alert for any signs of infection, sepsis, or septic shock when evaluating patients for renal failure, and, conversely, it is important to monitor renal function frequently (along with other organ involvement) in patients with documented or suspected sepsis.

Septic AKI is defined by AKI in the presence of sepsis without another significant contributing factor explaining AKI. Recent diagnostic and staging criteria for AKI included an absolute increase of serum creatinine concentration of 0.3 mg/dL over 48 hours, a relative change in serum creatinine concentration of 1.5 to 1.9 times baseline over 7 days, or a urine output of less than 0.5 mL/kg/h for 6 hours. The severity of septic AKI may be classified using the well-documented consensus KDIGO (Kidney Disease Improving Global Outcomes) criteria for AKI staging, and outcomes appear to correlate with the presence and severity of AKI as defined by this classification system.[2,19] Several pitfalls are associated with the use of serum creatinine value and urine output for the diagnosis of septic AKI. Serum creatinine is a late, insensitive marker of renal injury for a number of reasons. Because of the half-life of circulating creatinine, increments in serum creatinine concentration lag decrements in glomerular filtration rate by hours. Furthermore, the time to achieve a new steady-state concentration that fully reflects the degree of glomerular filtration rate loss is delayed by multiples of a prolonged serum creatinine half-life, reflected in changes over days rather than hours. In addition, in critically ill septic patients, hemodilution in hypotensive patients receiving aggressive fluid resuscitation with a positive fluid balance masks serum creatinine increments, and has been shown to delay AKI diagnosis by a further day. Sepsis also has been shown to reduce the muscular production of creatinine, even without weight loss, further reducing the utility of serum creatinine concentration as a marker of septic AKI.[20] Finally, patients receiving diuretics may not meet AKI diagnosis criteria based on reduced urine output owing diuretic action. Other urinary biochemistry indices (see later) may be similarly unreliable with diuretic use.

Early identification of AKI in septic patients is crucial because supportive and therapeutic maneuvers in septic patients often are nephrotoxic (eg, use of vancomycin and aminoglycosides; or the use of vasopressor therapy with inadequate fluid resuscitation) and can aggravate the renal injury. In most sepsis trials, septic AKI is associated with poor survival, which is influenced by the magnitude of renal recovery. A recent retrospective trial by Sood et al[21] showed that septic patients who experienced reversible AKI or improved AKI (within 24 hours of diagnosis) had better survival rates than patients who did not recover from AKI and even those who did not develop AKI at all. Factors independently associated with AKI reversibility in this study were early administration of antimicrobial therapy, lower Acute Physiology and Chronic Health Evaluation II score, younger age, and a smaller number of failed organs (excluding renal) on the day of shock, as well as community-acquired infection.

Additional tools may be useful to confirm or complement AKI diagnosis by determining differential

diagnostic and prognostic assessments. Urinalysis (by dipstick) and measurement of urine biochemistry indices such as the urinary sodium (UNa), fractional excretion of sodium (FeNa), and fractional secretion of urea (FeU) are used commonly to help differentiate prerenal AKI from acute tubular necrosis (ATN), but they remain insensitive and nonspecific tools, often offering little reliable information to AKI diagnosis. Their use in sepsis appears to be even more limited because septic AKI is a complex pathology that affects more than simply tubular reabsorption. A prospective cohort study of 83 patients failed to show any clinically significant differences among theses indices to help differentiate septic versus nonseptic AKI, and they were not predictive of AKI worsening, renal replacement therapy requirements, or death. Fifty percent of patients in this population showing significant microscopic evidence of tubular damage were found to have a FeNa concentration of less than 1%. Urine indices were not correlated with damage tubular marker such as NGAL.[22] In another study,[23] a low FeNa and FeU concentration were highly prevalent in the first hours of sepsis and a combination of both was predictive of transient AKI, whereas oliguria was predictive of impending AKI. These contradictions further question the use of urine biochemistry in critical care patients, especially in septic patients, because it may be unreliable as a result of the heterogeneity of kidney disease and the confounding factors (ie, timing, pre-existing chronic kidney disease [CKD], vasopressors, fluid resuscitation, or diuretics). Unfortunately, there is currently no urine biochemistry test available to differentiate septic AKI from nonseptic AKI accurately. A urinary scoring system based on the presence of granular casts and renal epithelial cells has been used to differentiate prerenal AKI and ATN with the presence of different types of urinary casts being associated with a higher likelihood of dialysis.[24] These urine microscopy scores also have been shown to be significantly higher in septic AKI patients than in nonseptic AKI patients. Urine microscopy scores also correlate well with urinary NGAL levels, more modestly with plasma NGAL, and are predictive of worsening AKI.[25] The use of urine microscopy for the diagnostic assessment of AKI is supported further by the potential to disclose significant treatable causes of AKI apart from prerenal azotemia or ATN, such as rapidly progressive glomerulonephritis (erythrocyte casts, active sediment with proteinuria, hematuria, leukocyturia) and allergic interstitial nephritis (leukocyturia, leukocyte casts in the absence of urinary tract infection, and perhaps with eosinophiluria). However, it must be emphasized that studies of urinalysis, biochemistry, and microscopy often are confounded by numerous factors such as the unknown timing of renal insult, varying degrees of sepsis severity, and fluctuating clinical course of different patients. All of these factors make interpatient and interstudy comparisons limited.

A promising investigational tool that allow earlier AKI diagnosis is the Doppler-based renal resistance index (RI). A higher RI may be predictive of AKI in patients with sepsis.[26] Doppler-based studies additionally may be useful in measuring renal perfusion during vasopressor therapy and may help to differentiate between transient and persistent AKI.[26–28] A major downfall in the clinical use of renal RI is that it is influenced by numerous factors including patient age, arterial stiffness, pulse intra-abdominal pressure, and other systemic hemodynamic factors such as pressure index, mean arterial pressure, and heart rate. In addition, these RI measurement results may differ between radiologists and centers and a comparison of results must take these factors into consideration. Data regarding the effect of systemic hemodynamics factors on RI still are contradictory, with influences seen in some studies and not in others.[26,28,29]

Most of these diagnostic tools remain imperfect and AKI diagnosis by serum creatinine increase or oliguria often is made after the window of opportunity for therapeutic or preventative intervention already has passed. For these reasons, newer biomarkers increasingly are being studied for rapid AKI diagnosis. These biomarkers can be classified as functional biomarkers (ie, serum creatinine and cystatin C) and as damage biomarkers (ie, urinary albumin, NGAL, interleukin-18, KIM-1 (Kidney injury molecule-1), L-FABP (Liver-type Fatty acid-binding protein-1), TIMP-2 (Tissue inhibitor of metalloproteinases-2), IGFBP7 (Insulin-like growth factor binding protein 7), and more). In addition to AKI, an increase of functional biomarkers with normal damage biomarkers may represent the prerenal state or in some cases CKD. On the other hand, an increase of damage biomarkers without an increase of functional biomarkers may represent a subclinical form of AKI that subsequently can progress into AKI as defined by a serum creatinine increase or resolve back to the normal state. The ultimate goal would be to have a marker for septic AKI that would help to identify the high-risk or subclinical AKI patients in whom prevention and support would play a critical role in outcome. These also would be the ideal patients to involve in interventional trials because they might benefit from the early treatment more than the patient with an advanced, acutely irreversible form of septic AKI. The concern with some of these biomarkers is that they are nonspecific to kidney injury and may be increased in sepsis without AKI. NGAL, for example, is released by activated neutrophils in response to infection. Interleukin-18 also is increased by inflammation and infection.[30] Several trials have evaluated the role of these biomarkers in septic AKI diagnosis. A pediatric

study showed increased and discriminatory levels of urinary NGAL and serum and urinary cystatin C in children with septic AKI compared with septic children without AKI. Serum NGAL levels were not different between these groups in this study and caution should be used when interpreting levels this biomarker in septic patients.[31] Results from an adult population trial confirmed the same findings, in which urinary NGAL and serum and urinary cystatin C showed significant discrimination for AKI in septic patients.[32] Urinary liver fatty acid–binding protein is significantly higher in ICU patients with AKI compared with patients without AKI, and has been shown to be predictive of mortality in septic patients.[33,34] Netrin, a laminin-like protein, may be an early marker of AKI. It appears to be excreted in the urine 1 hour after insult, reaching a peak 30-fold increase by 6 hours. This could represent an important opportunity for eventual early intervention in these high-risk patients. These results, although not consistent, appear to support the conduct of further studies of their general use, and perhaps will result in the development, validation, and implementation of diagnostic tools for early septic AKI diagnosis.[30]

The exact attribution of the etiology of renal injury in the septic patient may not always be as straightforward as one would wish. These patients often have a significant number of comorbidities (ie, immunosuppression, diabetes, hypertension, CKD, heart disease) and pre-existing medications (ie, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, calcineurin inhibitors, or others) that may contribute to the renal insult. Once hospitalized, patients often are exposed to additional risks and procedures, such as radiologic imaging or procedures requiring intravenous radiocontrast administration, or require specific treatment with nephrotoxic antimicrobial agents such as aminoglycosides or amphotericin B. Although we tend to limit the use of nephrotoxic agents, most, if not all, patients will receive antimicrobial therapy, which also rarely may cause an allergic interstitial nephritis. All of these interventions may cause hospital-acquired or iatrogenic AKI, which may contribute further or confuse septic AKI diagnosis. When there is doubt regarding AKI diagnosis, a renal biopsy should be considered. Histology studies in septic patients have shown an alternative diagnosis to acute tubular necrosis or normal renal histology (prerenal azotemia), including glomerular disease, acute interstitial nephritis, pyelonephritis, or signs of vascular disease (eg, atheroembolism).[35]

RESPONSE

Management of sepsis involves three aspects: prevention, treatment, and rehabilitation. Prevention remains the ultimate goal to reduce downstream patient and economic consequences and involves rapid treatment of infections, the development of preventative measures against hospital-acquired infections, glycemic control, and sometimes the use of prophylactic antibiotics. Sepsis-specific treatment has seen little progress since the discovery of antimicrobial therapy in the mid-1900s. For the moment, most of the available interventions for AKI are based on prevention of further renal insult or organ support. Timely recognition of sepsis and response is therefore the first key element in its treatment. Supportive treatment is key to preventing further organ damage and improving survival in sepsis. Early administration of appropriate antimicrobial therapy (within 6 hours and ideally within 1 hour) is the cornerstone of treatment in sepsis and improves survival.[36,37] In a multicenter retrospective cohort study with 3,373 hypotensive patients with septic shock, longer delays before administration of appropriate antimicrobial therapy were associated with early AKI development.[38]

Restoration of tissue perfusion and optimization of hemodynamic status are important goals of supportive therapy in sepsis and septic shock. Fluid therapy and vasopressor infusion are the main treatments available for hemodynamic support. Renal autoregulation of renal blood flow and glomerular filtration rate usually is maintained if mean arterial blood pressure (MAP) is in the range of 80 to 180 mm Hg. Within these values, fluctuations in blood pressure have only marginal effects on renal blood flow and glomerular filtration rate. Renal hypoperfusion, however, does not appear to be the main contributor to septic AKI.

Instead, human and animal studies have shown that renal blood flow in septic patients either was preserved or increased,[39–41] which strongly challenged the hypothesis that hypoperfusion resulting in either prerenal azotemia or ischemic renal injury with ATN are the predominant mechanisms of septic AKI. Of course, this also raises questions concerning the importance of a target MAP in septic patients, at least from a renal standpoint. There is currently no accepted bedside method to evaluate renal perfusion.

Early goal-directed therapy (EGDT) is an integrated approach designed to guide the physician with treatment goals and algorithms to treat septic patients. In 2001, Rivers et al[42] published a randomized, controlled, single-center emergency department trial of 263 patients in which they showed improved survival of patients with severe sepsis or septic shock treated with EGDT (targeting normalization of central venous oxygen saturation) within 6 hours of emergency room arrival, compared with patients treated with protocolized standard therapy (30.5% versus 46.5%). Soon after publication of the protocol of Rivers et al[42] it was integrated rapidly into the Surviving Sepsis Campaign

guidelines.[43] In addition to standard of care, the EGDT added serial measurements of central venous oxygen saturation ($Scvo_2$), which was used to guide treatment through fluid therapy, vasopressors, inotropes, and red blood cell transfusions to achieve an $Scvo_2$ higher than or equal to 70%. Unfortunately, renal outcomes were not evaluated in the seminal Rivers et al[42] EGDT trial. Renal outcomes have been evaluated in a small group of ICU patients treated with an EGDT protocol compared with historical controls, in a study that found a trend (that did not reach statistical significance) toward a lower AKI incidence in the EGDT group compared with standard therapy.[44] Since the publication of the initial EGDT study more than a decade ago, much progress has been made in the early recognition of sepsis, timely administration of antimicrobial therapy, and goal-directed or protocolized hemodynamic support, which has lead physicians to question if the results from this relatively small, single-center study still are applicable in modern practice. The ProCESS (Protocolized Care for Early Septic Shock) trial, a 31-center, randomized, controlled, emergency room trial, was designed to evaluate the generalizability and necessity of the 2001 EGDT protocol. Patients were randomized to one of three groups: EGDT, usual care, or a protocol-based standard therapy that did not involve central venous catheter placement, transfusion, or inotrope administration. There were no differences in 60-day, 90-day, and 1-year mortality among the three groups. New renal failure, defined here by the need for dialysis within the first week, appeared to be lower in the usual care group and the EGDT group compared with the protocol-based standard therapy (2.8% versus 3.1% versus 6.0%, respectively; $P = .04$). It must be mentioned that patients in the protocol-based standard therapy group received the greatest volume of fluid followed by the EGDT group and the usual care group. The duration of RRT did not differ among the groups.[45]

Advances in the care of ICU patients over the past decade such as implementation of lung-protective mechanical ventilation strategies, lower threshold for blood transfusion, and improved glycemic control may account for at least a part of the similarity in mortality rates in this study, rendering the contribution of EGDT less perceptible.

The Surviving Sepsis Campaign's most recent revision still recommends achieving a MAP of 65 mm Hg, a central venous pressure of 8 to 12 mm Hg when available, aiming for a urine output of at least 0.5 mL/kg/h and a $Scvo_2$ of 70% or higher.[37] It must be noted that these recommendations were published before the results of the ProCESS trial were available and evidence for use of $Scvo_2$ now is weaker and may not be included in the next guidelines. The group also recommends aiming for normalization of serum lactate levels. The Surviving Sepsis Campaign care bundle suggests administration of a 30 mL/kg crystalloid bolus for patients with hypotension within the first 3 hours and use of vasopressors within the first 6 hours for patients whose MAP remains less than 65 mm Hg despite fluid therapy. Formal evaluation of optimal fluid parameters or hemodynamic targets for AKI prevention or management has been limited. It was suggested in one study that targeting a MAP of 70 to 80 mm Hg would be necessary to prevent AKI in septic shock, but this needs further validation.[46] A recent multicenter study randomized 776 septic patients to resuscitation plus a high target MAP (80-85 mm Hg) versus a low target MAP (65-70 mm Hg). The 28- and 90-day mortality rates did not differ between groups. Interestingly, patients with pre-existing chronic hypertension in the high-MAP group required less RRT than patients in the low-target group.[47] The focus should be to restore organ perfusion, and treatment should be individualized according to patient comorbidities and clinical condition. Whether this should be achieved by fluid therapy or vasopressors depends on clinical evaluation of the patient's volume status. The optimal method for evaluating volume status is not well established.[48] Clinicians should rely on an ensemble of clinical findings as opposed to results from a single test and interpret them according to the patient's comorbidities and dynamic assessments of the patient's condition.

Fluid administration should be part of the initial therapy as recommended earlier, but should be re-evaluated serially during the day because septic alterations of hemodynamic status and vascular permeability is an evolving process. Septic AKI patients tend to have lower urinary outputs, receive more fluid therapy and/or diuretics, and are more likely to develop fluid retention than nonseptic AKI patients.[38,49,50] Fluid overload has been associated with worse patient outcome in numerous studies.[50,51] A recent retrospective trial by Legrand et al[52] identified an association between new or persistent AKI and increased central venous pressure. These findings go against the previous belief that when it came to fluid administration in septic patients, there was no such thing as less is more. A high central venous pressure is no longer a desirable target and fluid resuscitation–induced venous congestion increasingly is believed to be contributing to renal injury.[53] In light of this information, it would be advisable that boluses should be administered at patient presentation and then fluid responsiveness should be evaluated within a few hours. Crystalloids are the fluid of choice for resuscitation and hydroxyethyl starches or hyperchloremic solutions are not recommended.[37] Numerous trials have evaluated the use of synthetic colloids in the past decade. A 2013 meta-analysis of these has shown increased association with RRT

requirements with no shown benefit on survival. Septic patients treated with hydroxyethyl starches also appear to develop more AKI and have increased requirements of RRT.[54] Fluid administration should be tempered after the initial bolus phase and eventually ceased when the patient reaches an equilibrium phase, after which the aim should be fluid mobilization by withholding fluids and allowing diuresis (spontaneous or with diuretics as needed). It should be noted that if at any time the patient appears unresponsive to fluid therapy, then vasopressors should be prioritized over fluid therapy to avoid unnecessary fluid accumulation. Vasopressor support often is needed in septic shock because fluid therapy alone does not correct sepsis-induced systemic vasodilatation and endothelial dysfunction. Norepinephrine is the drug of choice for septic patients requiring vasopressors.[55] Vasopressin has been compared with norepinephrine and did not appear to offer any benefit on mortality.[56] This study, however, noted that patients with mild forms of AKI were less likely to progress to more severe AKI, but this was observed in a post hoc analysis (Fig. 3).[57]

Another key element in the management of septic patient in regard to AKI prevention is the avoidance of potentially nephrotoxic medication and contrast agents when possible, especially in high-risk patients (ie, diabetes, older age, or CKD).[58,59] Fenoldopam, a vasodilator with immunologic properties, has been tried as a preventive treatment in numerous AKI etiologies including sepsis, which has shown conflicting results and currently is not recommended in practice.[60,61]

The enzyme alkaline phosphatase (AP) has shown promising results in the treatment of sepsis, predominantly through a renal protective effect in two phase 2a trials.[62,63] In these trials, the administration of AP prevented septic AKI development and reduced the severity of AKI when it was present, with few patients requiring RRT, a shorter duration of RRT, and better creatinine clearance. It is believed that AP reduces inflammation through dephosphorylation and therefore detoxification of endotoxins and conversion of adenosine triphosphate into a form of adenosine with anti-inflammatory and tissue-protective effects. These two mechanisms are believed to work against the hypoxic and inflammatory injuries encountered in septic AKI. Pharmacologic properties and the safety of AP have been tested.[64] In light of this, AP can be considered a potential future treatment for sepsis-induced AKI if pivotal confirmatory clinical trials are similarly successful.[65]

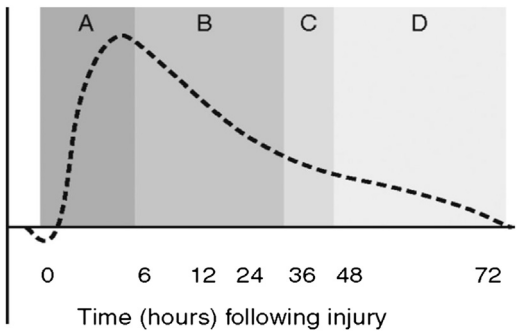

Figure 3. Fluid resuscitation strategy during the stress response. Phase A: 0 to 6 hours, indicates aggressive volume resuscitation. Phase B: 6 to 36 hours, indicates decelerating fluid resuscitation; fluid boluses should be administered to compensate for extravascular sequestration. Phase C: 36 to 48 hours, indicates the equilibrium phase; stop administering intravenous fluids. Phase D: 48 to 72 hours, indicates mobilization fluids; withhold fluids and allow spontaneous diuresis (or diurese if necessary).

Nutritional support is an important but often overlooked aspect of global patient care. It is especially important in septic AKI, a hypercatabolic state that requires adapted protein and caloric intake. Numerous aspects need to be considered when calculating a septic AKI patient's nutritional requirements such as his baseline characteristics, underlying condition, volume status, and possible protein loss through RRT. For these reasons, each patient requires an individual approach for nutritional support.[66–68]

EXTRACORPOREAL BLOOD PURIFICATION

The utility of extracorporeal blood purification therapies for septic patients can be evaluated (and debated) for two different purposes: renal support and immunomodulation therapy.

The first and more commonly used application is renal replacement therapy in patients whose renal function fails to provide sufficient function to maintain body homeostasis. Traditional RRT indications for organ support purposes such as uremia, metabolic disturbances, and fluid overload apply in septic AKI just as in nonseptic AKI. The timing of RRT initiation remains heterogeneous in clinical practice and is not yet firmly supported by uniform scientific evidence although excessive delays have been linked to higher mortality rates and worse renal function in a retrospective analysis including septic patients.[69] The only published randomized controlled trial available to date did not find significant differences in renal outcomes or patient survival between early and late initiation of hemofiltration.[70] Two trials now are ongoing and hopefully will answer the optimal RRT timing question: STARRT-AKI (Standard versus accelerated initiation of renal replacement therapy in acute kidney injury) trial[71] and the IDEAL-ICU (Initiation of dialysis early versus late in intensive care unit) study.[72] The latter is addressing this question specifically in septic AKI patients.

The RRT modality choice may have important implications for survivors of septic AKI because

continuous renal replacement therapy (CRRT) appears to be associated with better renal recovery than intermittent modalities.[73,74] Along the same lines, a recently published retrospective study of septic AKI patients from China found that initial therapy with continuous venovenous hemodiafiltration (CVVHDF) was associated with greater renal recovery at 60 days (defined as dialysis independence) compared with patients treated with extended daily hemofiltratrion.[75] This difference was observed despite the fact that CVVHDF patients had lower blood pressure and were more acidotic and oliguric than the other group treated with extended daily hemofiltration. Although they did not observe a significant difference in mortality, the difference in dialysis dependence observed remains a relevant clinical outcome.

Although CVVHDF is more costly than intermittent dialysis modalities in the ICU, the development of end-stage renal disease requiring chronic dialysis, high cost to society, was lower in the long term. The differences in renal recovery may be owing to the better fluid control that was achieved with fewer episodes of hypotension with CRRT.

Optimal RRT dosing was evaluated in two major critical care trials (without specifically focusing on AKI) and the current recommended adequate effluent rate (delivered RRT dose) for CRRT is 25 to 30 mL/kg/h.[76–78] In one of these trials, a post hoc analysis of septic patients showed a tendency toward reduced a mortality rate in the group or patients treated with the higher-intensity approach (40 versus 25 mL/kg/h).[70] Clinicians must take into consideration the fact that prescribed and delivered CRRT doses may differ because treatment is interrupted for numerous reasons during a patient's stay and therefore clinician's should overprescribe with a 25% safety margin (30-35 mL/kg/h) to ensure an adequate delivered dose.[78,79] High-volume hemofiltration is defined as an effluent rate greater than 35 mL/kg/h, although some advocate that the criteria for this definition should be higher. High-volume hemofiltration has been hypothesized to clear sepsis-associated inflammatory mediators and therefore perhaps help to reduce inflammation-induced organ damage and improve septic shock survival. Because CRRT at a standard renal-dose does not appear to improve outcomes in septic shock without renal failure,[80,81] studies using higher effluent rates (70-85 mL/kg/h) have been conducted to evaluate this approach. These trials and a recent meta-analysis all have failed to show any impact on patient survival, hemodynamic status, or organ improvement.[82–84] Two possible factors explaining the absence of a significant difference in outcomes in high-volume hemofiltration trials are the low cut-off points of the hemofilters used (which do not remove larger mediators), and the technical difficulties in delivering and maintaining the prescribed CRRT dose.

REHABILITATION AND FOLLOW-UP EVALUATION

Early detection and reversal of AKI was associated with better outcomes.[18] In addition, a prospective observational international study of 1,753 patients showed that patients with septic AKI showed a trend toward higher chances of recovery and dialysis independence compared with nonseptic AKI patients, even though they had a higher risk of death and a longer hospital length of stay.[85]

Although survival data are available, the renal prognosis of septic AKI has not been well described in the literature. Renal recovery is highly unlikely when sepsis is not controlled because the mechanisms of insult persist. Once sepsis is resolved, the likelihood of renal recovery depends on a number of factors such as the patient's underlying characteristics (age, underlying CKD, diabetes, and other comorbidities), the severity of underlying insult (prolonged hypotension, sepsis severity, and multiple organ involvement), and the iatrogenic insults associated with the process of care (fluid overload, hypotension associated with RRT, nephrotoxic antibiotics, or contrast exposure). In clinical practice, the kidney is often one of the last organs to recover in patients with multiple organ failure caused by sepsis, and patients may require weeks to months of dialysis.

Patients should be monitored for renal recovery during their hospital stay, before hospital discharge, and, if no recovery has occurred by that time, renal recovery also should be assessed at regular intervals after discharge. We suggest that a useful way of monitoring renal recovery in these patients would be timed urinary creatinine and urea clearances repeated at periodic intervals.

As for all AKI cases, septic AKI patients should be scheduled for follow-up evaluation within 3 months as suggested by the KDIGO AKI clinical practice guidelines to monitor kidney function and address recovery or optimize CKD treatment.[24]

RESEARCH

The incidence of sepsis has been increasing by 8.7% yearly and the mortality rate has not changed.[86] Despite all the progress achieved in general medicine in the past decades, the mortality rate of septic AKI remains unacceptably high. Contributing factors to this dilemma are perhaps the fact that the underlying pathophysiology of septic AKI still is not fully understood with complete histologic information, and that the tools currently used to assess it (serum creatinine and urine output) are of relatively low reliability in the septic patient. Despite numerous trials attempting to find a pharmacologic treatment for septic AKI, very few have been successful. This may be owing to several factors such as late recognition of AKI, by

which time significant renal damage already has occurred. Another important factor to be considered is the heterogeneity of the septic population being studied, with variable organ involvement and multiple possible pathogenetic factors contributing to renal injury.[87] As mentioned earlier, early identification of high-risk patients may be the key to preventing septic AKI and ultimately obtaining significant results in AKI treatment trials.

Future research should focus on two major aspects of prevention and treatment of septic AKI: identification of high-risk patients at earlier stages of renal injury, and targeted treatment of AKI once it has developed. Novel biomarker and imaging studies should be designed to select patients with early injury, to facilitate the design of specific therapeutic trials and complement clinical ascertainment of modifiable patient risk factors. Another key in septic AKI prevention is the establishment of appropriate criteria for surveillance of septic AKI in hospitalized patients, whether it be through pharmacy identification of high-risk medication in a patient's profile, judicious use of contrast in patients at high risk of contrast-induced AKI, or careful use of fluid, diuretics, and nephrotoxic medication. Further understanding of underlying pathophysiologic models of septic AKI will be crucial to achieve successful prevention and therapeutic trial designs and results.

CONCLUSIONS

AKI associated with sepsis may present in different forms and is associated independently with increased mortality and morbidity. AKI may precede or follow sepsis. Differentiating septic AKI from other forms of AKI is important because underlying pathophysiologic mechanisms and outcomes differ between these two groups. The identification of high-risk patients and those with early AKI is crucial in influencing patient outcome. Serum creatinine and urine output are imperfect markers of early AKI in septic patients, and other novel tools need to be implemented to identify these patients. Although there are no specific treatments for septic AKI, early antibiotic administration, avoidance of hypotension (through fluid administration or vasopressors), nephrotoxic agents and fluid overload (through judicious use of fluid therapy, diuretics, and RRT) can minimize AKI risk. CRRT has been associated with improved renal recovery, and perhaps should be started earlier in AKI evolution, but this needs to be validated in future studies. Future trials should be designed to identify high-risk patients with early injury and focus on targeted therapy.

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