Potential Interventions in Sepsis-Related Acute Kidney Injury

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Sepsis is an important cause of morbidity and mortality. Acute kidney injury often complicates sepsis, leading to greater complexity, cost of care, and worsening prognosis. In recent years, a consensus definition of acute kidney injury has been developed, facilitating research into the pathophysiology and epidemiology of this disorder. New and emerging biomarkers to recognize kidney injury before functional abnormalities are manifest may allow early recognition and facilitate prevention or treatment. Furthermore, advances in the clinical management of sepsis may have secondary benefits with respect to renal outcomes. Existing and hybrid extracorporeal therapies are being investigated not only as means to replace lost kidney function but also to modulate the immune response to sepsis. For those who have more advanced forms of kidney injury, strategies to promote renal recovery are being sought to minimize the long-term consequences of impaired kidney function. This review provides an update on the current state of the science and a glimpse toward the future of intervention in sepsis-related acute kidney injury.


The pathophysiology of sepsis is complex and multifactorial. In critically ill patients, this disorder typically produces multiple-organ dysfunction. Among the several disorders encountered in sepsis, acute kidney injury (AKI) is one of the most important because it is a life-threatening condition, increases the complexity and cost of care, and is an independent risk factor for mortality (1,2). The potential interventions in sepsis-related AKI consist of (1) effective prevention/protection strategies for the kidney in patients at risk, (2) early recognition and attenuation of renal damage, (3) pathophysiology-driven pharmacologic support, (4) efficient extracorporeal blood purification therapy, and (5) strategies that promote recovery of renal function.

Pathophysiology and Classification of Sepsis-Induced AKI

AKI is a complex disorder that until recently lacked a widely accepted definition. This has impeded comparisons of articles in the literature and has limited the ability to develop effective approaches to prevention and treatment of AKI. Having a uniform standard for the diagnosis and classification of AKI is therefore vital. A consensus-based definition and classification system has been proposed whereby diagnostic criteria based on creatinine change and/or urine output changes are used to classify different levels of injury (3). Recently, these different levels of injury, characterized by the acronym RIFLE (risk, injury, failure, loss, ESRD) have been shown to correlate with morbidity and mortality in a stepwise manner in a number of studies (4–7). AKI, as defined by the RIFLE criteria, is now recognized as an important intensive care unit (ICU) syndrome alongside other defined syndromes such as systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock (8) and acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (9).

It is worth noting that the RIFLE classification of AKI was originally intended to standardize the severity and definition of AKI, providing an important tool for research. Notwithstanding the ability to predict outcome, it is not intended to take into account the cause of AKI or the need for renal replacement therapy (RRT). Other limitations include issues surrounding the differing sensitivity and specificity of the urine output criteria compared with the change in serum creatinine, although the former adds important information in the evaluation of patients (6). The validity of estimating baseline creatinine when this value is unavailable has also been raised as a concern. These limitations and others are highlighted in a recent systematic review by Ricci et al. (10). Recently, the Acute Kidney Injury Network proposed a new staging system for AKI, with stages 1, 2, and 3 corresponding to the risk, injury, and failure categories. Slight modifications to the criteria for stage 1 result in even greater sensitivity for the diagnosis of early AKI, and categories for loss and ESRD have been eliminated because these represent outcomes (11). Whether these modifications are an improvement to the existing RIFLE clas-
sification or will demonstrate a high false-positive rate requires further study.

AKI in sepsis seems to have a multifactorial pathogenesis, which is summarized in Figure 1. Although sustained global or regional hypoperfusion, with ischemia and subsequent reperfusion, is thought to be a major triggering event in eliciting AKI, an increasingly important role for apoptosis in septic AKI is being recognized (12). Although there is no gold standard to evaluate reliably global and regional renal perfusion at the bedside, exciting new imaging techniques such as magnetic resonance imaging hold promise in human studies in terms of identifying altered function and sites of inflammation and apoptosis, whereas innovations such as intravital multiphoton microscopy are allowing researchers to understand better the temporal and causal relationships of hypoperfusion, inflammation, and apoptosis in animal models of AKI (13–15). Molitoris (16) illustrated the phases of ischemic acute renal failure, dividing them into initiation, extension, maintenance, and recovery, and indeed this paradigm can be extended to overlap with processes in septic AKI. For instance, Wu et al. (14) identified early severe reduction of peritubular capillary perfusion leading to tubular injury in a rodent cecal ligation and perforation model of sepsis using intravital videomicroscopy, but ongoing endothelial dysfunction, with loss of regulation of vascular tone, perfusion, permeability, inflammation, and adhesion, would lead to extension of this injury as proposed by Molitoris and Sutton (17) in their work on ischemic acute renal injury.

In addition, recent insights have moved us away from the simplistic view of sepsis-related AKI as simply a combination of hypoperfusion and a proinflammatory state of an “immune system gone haywire” (18). It is likely that elevated and imbalanced pro- and anti-inflammatory mediators, the so-called “peak concentration hypothesis” (19), coupled with severe endothelial dysfunction and a perturbed coagulation cascade operate synergistically to induce chemically and biologically mediated kidney injury. Recent animal models of sepsis-related AKI demonstrated the importance of these factors beyond simple hypoxic/ischemic injury (20–22), whereas the peak concentration hypothesis provides a rational paradigm for the use of broader spectrum immunomodulatory therapies such as extracorporeal blood purification, as depicted in Figure 2. On the basis of this pathophysiologic understanding, different interventions can be proposed to avoid, mitigate, or stabilize AKI and possibly to support or replace lost kidney function, bridging the organ to and facilitating the potential for renal recovery.

Prevention/Protection Strategies

An effective prevention strategy is difficult to implement in sepsis because significant renal damage might have already occurred before overt signs and symptoms of sepsis and septic shock appear. Nevertheless, in patients at risk, different nephroprotective drugs have been proposed on the basis of various physiologic rationales. Unfortunately, only discouraging results from these drugs have been achieved so far, and real prevention has not been possible. Nevertheless, because AKI derives from a common pathway combining inflammation and toxicity, it would seem imperative to maintain renal blood flow to avoid further injury even if the initial injury is not mediated by ischemia. In sepsis, the primary threats to renal blood flow are derived from reduced cardiac output, typically secondary to reduced effective intravascular volume and renal perfusion pressure, although cardiac output may vary during different phases of the process of sepsis. In fact, a preferred animal model of sepsis is the cecal ligation and perforation model, which more closely mimics human sepsis than simple administration of lipopolysaccharide and indeed leads to an early hyperdynamic phase characterized by decreased peripheral vascular resistance and increased cardiac output (23). Langenberg et al. (24) highlighted the complex relationships between cardiac output and renal vascular resistance in a recent exhaust-
tive review of the literature in both animal models and human studies of sepsis. Unfortunately, much of what has been published in terms of renal perfusion in sepsis derives from animal studies, with significant differences in methods and hence heterogeneity of results. Furthermore, maintenance of normal or even increased renal blood flow provides no guarantee against altered perfusion at the level of the microvasculature (23). For instance, in a recent large animal model of sepsis, Langenberg et al. (25) demonstrated worsening renal function in the context of increased renal blood flow.

The role of fluid and hemodynamic management in human clinical trials is an area in which timing and goals are not straightforward. The Surviving Sepsis Campaign recommends that extracellular volume and cardiac output be assessed and supported with adequate and early goal-directed therapy (26). This includes volume and pressor support to achieve a mean arterial pressure $\geq 65$ mmHg and a central venous pressure of 8 to 12 mmHg (or 12 to 15 mmHg in patients who receive positive pressure ventilation) (26,27). The importance of early goal-directed therapy is supported by work done by Rivers et al. (28), who, in a single-center study, demonstrated that early versus delayed administration of fluid, vasopressors, blood products, and inotropes to maintain central venous oxygen saturation of $\geq 70\%$ had important benefits in terms of mortality and multiorgan failure. This is in contrast to an earlier study (29) in which therapies directed to maintenance of a target cardiac index or mixed venous oxygen saturation in patients with established sepsis did not improve outcome. These observations highlight the importance of early initiation of resuscitation. Fluid administration is essential to restore effective circulating volume but should stop when patients are no longer fluid responsive—assessed either by direct measures of cardiac output or by pulse-pressure variation (30).

Choice, timing, and amount of fluid administration are also emerging as important determinants of AKI, with some concerns raised over the use of certain forms of colloid, namely hydroxyethyl starch (31–33). In a randomized study of septic patients, Schortgen et al. (34) found that patients who were randomly assigned to hydroxyethyl starch had a much higher risk for acute renal failure, oliguria, and higher peak creatinine than those who were randomly assigned to gelatin. Results of the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial, which was discontinued early after interim analysis, are expected to shed further light on the risks of this particular colloid (32,35); however, it should be noted that stanches vary in their composition, and whether the risks of one formulation can be extrapolated to all is hotly debated (35,36). In terms of albumin, results of the Saline versus Albumin Fluid Evaluation (SAFE) study, a randomized comparison of human albumin with crystalloid in the ICU, seem to indicate that albumin is safe, albeit no more effective than saline, for fluid resuscitation (37). That being said, in a predefined subgroup with sepsis (approximately 18% of the total population), the SAFE study found a trend toward improved survival in the albumin group, with a relative risk of 0.87 (95% confidence interval 0.74 to 1.02; $P = 0.09$). Whether this is simply the play of chance or a real finding would require further study in this population.

It is important to note that there is conflicting evidence that achieving supranormal hemodynamic values in these circumstances protects the kidney. The negative study of goal-directed therapy in established ICU patients (29) stands in contrast to a more recent study of protocol-driven therapy in patients who had septic shock and were transferred to an ICU from both the emergency department and the in-patient ward. In this latter study, Lin et al. (38), who did not have ready access to measures of central venous oxygenation, randomly assigned 224 patients with sepsis and systolic BP $\leq 90$ mmHg to standard therapy versus protocol-driven maintenance of central venous pressure from 8 to 12 mmHg, mean arterial pressure $\geq 65$ mmHg, and urine output $\geq 0.5$ ml/kg per h and demonstrated reduced mortality, decreased ICU length of stay, and decreased ventilator days. Of relevance to the kidney, the incidence of acute renal failure fell from 55.2% in the standard group to 38.9% ($P = 0.015$). Unfortunately, the study by Rivers et al. (28) of early goal-directed therapy did not specifically address the issue of AKI. Nonetheless, a recent report from this group (39) demonstrated the importance of this strategy in improving a number of biomarkers of sepsis, including those associated with global tissue hypoxia, so it is possible that the kidneys benefit from early aggressive fluid resuscitation. The other noteworthy observation in these trials was that goal-directed therapy could be achieved with a central venous catheter and that a pulmonary artery catheter was not required, reducing the complexity of care. These results are consistent with the recent randomized comparison of these catheters in management of ALI (40).

In addition to supporting cardiac output and extracellular fluid volume, attention should be focused on maintaining renal perfusion pressure. To achieve adequate renal perfusion pressure, patients with sepsis often require vasopressor support, because fluid alone does not correct the systemic vasodilation derived from endothelial dysfunction and nitric oxide release. Norepinephrine seems to be the drug of choice when volume and cardiac output have been corrected and significant vasodilation impedes the achievement of an adequate renal perfusion pressure. Despite concerns about vasoconstriction from norepinephrine leading to decreased renal perfusion and worsening renal function, the opposite has in fact been demonstrated (41), and norepinephrine is considered to be a first-line agent for the management of hypotension in sepsis (26). In septic shock, vasodilation, particularly through increased synthesis of nitric oxide, occurs through multiple mechanisms and may be hyposensitive to catecholamines (42). Furthermore, the presence of high levels of endogenous (and exogenous) catecholamines can lead to desensitization of adrenergic receptors. These observations, coupled with innately low levels of endogenous vasopressin, have led to the notion of using exogenous vasopressin and its analogues in the management of septic shock (42,43). In a small, pilot, randomized, controlled trial of 24 patients with severe septic shock, the use of vasopressin led to improved urine output, an increase in creatinine clearance of approximately 75%, and decreased overall pressor
requirement, whereas no such improvement was seen in the comparator arm of norepinephrine (44). Notwithstanding this and other encouraging small studies, the Surviving Sepsis Campaign recommended reserving vasopressin for refractory shock (grade E) at low dosages of 0.01 to 0.04 U/min, pending the results of ongoing clinical trials such as the Canadian Vasopressin and Septic Shock Trial (VASST) (26,43). Preliminary results of this randomized, blinded trial, conducted in nearly 800 individuals, showed decreased open-label pressor requirements in the vasopressin group but no difference in mortality or organ dysfunction; however, in a predefined subset of patients with less severe septic shock, both 28- and 90-d mortality were improved by an absolute amount of approximately 10% (45). The full peer-reviewed manuscript is eagerly anticipated.

For the critically ill patient, particular mention should be made of the effect of possible increases in abdominal pressure as a result of abdominal compartment syndrome (46). This condition can increase venous pressure to a point at which perfusion is impaired. Correction of this problem should then be immediately considered because AKI rapidly develops under these circumstances. Recently, evidence has emerged that renal injury can be reduced by supportive therapy aimed at metabolic control and remote organ protection. Two strategies in particular seem to have promise: Tight glucose control with insulin and reduction in tidal volume on mechanical ventilation.

**Tight Glucose Control**

The use of aggressive insulin therapy aimed at achieving euglycemia in critically ill patients has been shown in a single-center study to reduce mortality significantly in critically ill, mechanically ventilated surgical patients with a septic focus (47). Among the other important findings of this trial was a dramatic reduction in the development of severe acute renal failure that required RRT (8.2 versus 4.8%; P = 0.04) and a reduction in the number of patients who experienced a peak creatinine >2.5 mg/dl or a peak urea nitrogen of >54 mg/dl. In a subsequent study from this group in medical patients in the ICU, mortality was not improved, but there was an important reduction in the risk for AKI defined by I or F criteria of RIFLE (8.9 versus 5.9%; P = 0.04) (48). A possible explanation for this finding may relate to the fact that insulin may play an important anti-inflammatory role in sepsis (49–52). Thus, some of the beneficial effects of insulin therapy may be immune in origin rather than endocrine in nature. As such, they would fit in well in the paradigm that septic AKI or AKI of critical illness may represent an immunologic/toxic state. It is also of interest that insulin has a powerful antiapoptotic effect (49) and that, conversely, high glucose concentration induces oxidative stress-mediated apoptosis in tubular epithelial cells (49). A very large, multicenter, randomized, controlled study to assess the effectiveness of intensive insulin therapy in critically ill patients is under way (53) and will likely further increase our understanding of whether tight glucose control does indeed benefit the kidney in critical illness and sepsis.

**Low-Tidal-Volume Ventilation and AKI**

Ventilation of patients with ARDS by means of a low-tidal-volume strategy has been shown to reduce mortality (54). The mechanisms for such reduced mortality, however, remain unknown. It is possible that protective ventilator strategies might affect the well-being of other organs. In a fascinating series of studies, Imai et al. (55) demonstrated that low-tidal-volume ventilation might protect the kidney from injury in the setting of experimental and clinical ARDS. Using a rabbit model of ARDS, these investigators found that animals that were randomized to an injurious ventilator strategy had increased epithelial cell apoptosis in the kidney as well as the small intestine. Furthermore, such animals had evidence of renal dysfunction. When renal cells were incubated *in vitro* with plasma from rabbits that were exposed to an injurious ventilator strategy, apoptosis of such cells was induced and was markedly greater than that seen with exposure to control plasma. These investigators hypothesized that Fas ligand might be responsible for these changes and used Fas-Ig (a fusion protein that blocks soluble Fas ligand) to test this hypothesis. They found that Fas ligand blockade attenuated *in vitro* apoptosis of renal cells. To confirm further such association, they obtained plasma from patients who were enrolled in a previous ARDS study that compared low-tidal-volume ventilation with traditional tidal volume ventilation and found that there was a significant correlation between Fas ligand levels in plasma and serum creatinine.

An additional link between lung function and kidney injury was demonstrated in the randomized trial of conservative versus liberal fluid management in patients with established ALI (56). The conservative strategy resulted in fewer ventilator days and shorter ICU stays. Amid concerns that the former might compromise renal perfusion and cause or aggravate kidney injury, the conservative group did have higher levels of creatinine, urea, and bicarbonate; however, the trend was for dialysis treatments to be more common in the liberal strategy (14 versus 10%; P = 0.06), suggesting that improved lung function and oxygenation was beneficial to the kidneys and other extrapulmonary organs.

**Early Recognition of Renal Damage and New Biomarkers**

According to RIFLE criteria, AKI can be diagnosed by small changes in serum creatinine or acute reductions in urine output (3). Because of such sensitivity, the RIFLE criteria have enabled us to diagnose AKI in its relatively early stages. Nevertheless, when creatinine is rising and renal injury has been detected, some of the interventions may still lack efficacy because of the loss of an appropriate therapeutic window. For this reason, an even earlier detection of renal injury (before any functional abnormalities manifest) may be required to deliver therapies at a sufficiently early time during the process of renal injury. One potential solution is the use of *“early”* biomarkers of renal injury. Recently, molecules such as kidney injury molecule-1 or neutrophil gelatinase associated lipocalin (NGAL) demonstrated a good correlation with subsequent kidney damage (57) and hence their potential in assisting not only with diagnosis but also with earlier therapeutic interventions. Other molecules
are under scrutiny, and this approach will likely contribute to determining the timing and the level of kidney damage, especially during well-defined procedures such as radiocontrast exposure or cardiopulmonary bypass. For example, recent studies have shown that urinary NGAL is upregulated early (within 2 h) after murine renal injury, in a dosage-dependent manner (58). The same molecule was observed to increase in the urine and plasma of children with AKI after cardiac surgery (59). Initially discovered in neutrophils, this 25-kD secretory protein was later shown to accumulate extensively in the kidneys after ischemic renal injury (60). NGAL may attenuate renal injury as a result of experimental ischemic acute renal failure, by reducing apoptosis and enhancing proliferation of renal tubules, which are the most significantly injured structures (60,61). This effect is achieved possibly because NGAL augments iron delivery to proximal tubular cells, and iron in turn upregulates hemeoxygenase-1, an enzyme that protects tubular cells (60). Independent of iron transport, NGAL can additionally promote renal tubule formation and might enhance tubule repair after AKI (61). Urinary or plasma NGAL may, therefore, be a useful early biomarker of acute renal dysfunction. Prospective multicenter studies in large unselected populations of various ages are needed to validate these early observations.

Another potential strategy for early recognition of impending or early kidney injury is the use of rapid determination of GFR. Several investigators have demonstrated real-time changes in renal function using thermodilution techniques, although this is an invasive procedure, requiring placement of a catheter in the renal vein (62). Others have shown a strong correlation between sparse blood sampling after administration of iodinated contrast compared with the gold standard of inulin clearance (63), although concerns about the use of contrast in the context of patients who are at risk for AKI suggest a limited role for this approach. Others have looked at radioactive and nonradioactive means of continuously monitoring renal function in the ICU (15), including a noninvasive bedside radiation detector the size of an automated BP cuff (64). Finally, investigators have used serum cystatin C measurements to identify early and small changes in renal function in the ICU (65,66), identifying AKI according to RIFLE criteria sooner than using the creatinine criteria, with excellent diagnostic accuracy (65).

**Pharmacologic Support**

Several drugs have been proposed to protect the kidney and may affect the course of AKI. For decades, diuretics have been used either alone or in combination with other agents, in patients with AKI, yet improvements in survival or renal recovery have yet to be shown by high-quality studies (67–69) with some suggesting the potential for harm. Loop diuretics act at the medullary thick ascending loop of Henle to inhibit the Na⁺ / K⁺ / 2Cl⁻ pump on the luminal cell membrane surface and reduce oxygen demand (70,71). For this reason, it has long been held that the timely use of loop diuretics might attenuate the severity of AKI. Furthermore, diuretics could potentially play a vital role in managing extravascular volume overload by augmenting urine output and aid in acid-base and potassium homeostasis. Small clinical studies have suggested that diuretics might improve renal prognosis by converting “oliguric” to “nonoliguric” AKI, shortening the duration of AKI, or even improving the rate of renal recovery, and perhaps delaying or decreasing the need for RRT (69,72–76); however, these studies are countered by others that question the utility and safety of diuretics in the management of AKI-associated volume overload (77–80). Thus, although there seems a biologic rationale for their use, there is a limited understanding of how and when diuretics should be used or whether they should be used at all. There is also uncertainty about whether clinicians have genuine equipoise for the conduct of a randomized, controlled trial to assess diuretics in AKI (79).

For many years, dopamine held a prominent place in the prevention and management of AKI, despite a lack of proven benefit. Recent work finally demonstrated that dopamine is clearly not effective in preventing or treating AKI (81,82). Fenoldopam, a complex agent that can act at the hemodynamic level as well as have immunologic properties, was recently studied as a prophylactic treatment in patients with sepsis. In a single-center, double-blind, randomized, controlled trial of 300 patients with severe sepsis, Morelli et al. (83) found that prophylactic administration of fenoldopam was associated with some attenuation in the degree of subsequent renal dysfunction. Although these results are promising, they require confirmation in larger multicenter studies, and optimism is tempered by the fact that fenoldopam is closely related to dopamine. Encouraging, however, is that new treatment concepts for AKI, particularly in sepsis, are emerging.

**Activated Protein C**

Activated protein C (APC) is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation. During sepsis, reduced levels of APC are associated with increasing risk for death. Bernard et al. (84) showed a significant decrease in 28-d mortality (30.8% in the placebo group and 24.7% in the drotrecogin α activated group) in 1690 patients with sepsis. The efficacy of APC in patients with sepsis may be due to its anticoagulation effect; however, a study by Joyce et al. (85) showed that recombinant human APC directly modulated patterns of endothelial cell gene expression, clustering into anti-inflammatory and cell survival pathways, and modulated several genes in the endothelial apoptosis pathway, including the Bcl-2 homologue protein, an inhibitor of apoptosis. More recently, Cheng et al. (86) showed that APC blocks p53-mediated apoptosis of human brain endothelium in vitro. APC normalized the Bax/Bcl-2 ratio and reduced caspase-3 signaling. This study creates a new link among coagulation, inflammation, apoptosis, and cell death and provides insight into the molecular basis for the efficacy of APC in systemic inflammation and sepsis. Simultaneously, at a clinical level, there has been much controversy about the efficacy of APC (87). Such controversy has led to calls for more randomized, controlled studies of patients with sepsis. In a recent editorial, Eichacker and Natanson (88) put into context the results of a number of randomized trials as well as recent clinical surveys, suggesting that the significant “real-world” bleeding risk needs to be considered as we try to identify the type of patient who is likely to reap
the clinical benefits. A large, randomized, controlled trial of patients with multiorgan failure is in the developmental phase.

**Caspase Inhibitors**

Caspases are enzymes that are believed to play a key role in apoptosis. Caspase inhibitors have been developed as anti-apoptotic agents. Fauvel et al. (89) developed an animal model of myocardial dysfunction after endotoxin administration. They successfully used a broad-spectrum caspase inhibitor (z-VAD.fmk) and a caspase-3-inhibitor (z-DEVD.fmk) and demonstrated decreased myocardial dysfunction, reduced caspase activation, and reduced apoptosis 2 h after experimental endotoxemia. Neviere et al. (90) used z-VAD.fmk 4 or even 14 h after endotoxin administration in rats and showed not only that there was reduced caspase activity and apoptosis but also that endotoxin-induced myocardial dysfunction could be completely prevented. Because sepsis-related myocardial dysfunction can be prevented by antiapoptotic treatment, it is conceivable that the kidney is another organ that could benefit from caspase inhibitors. Indeed, Du et al. (91,92), in a series of experiments in murine tubular epithelial cells, demonstrated the central role of caspase-8 in mediating apoptosis in response to exogenous nitric oxide or cytokine-induced nitric oxide synthesis. Furthermore, epithelial cell apoptosis could be blocked by caspase-8 inhibition using z-IETD-fmk or caspase-8 silencing with short hairpin RNA or through overexpression of the endogenous caspase-8 inhibitor cellular Flice-inhibitory protein, suggesting that caspase-8 inhibition using z-IETD-fmk or caspase-8 silencing can be prevented by antiapoptotic treatment, it is conceivable that the kidney is another organ that could benefit from caspase inhibitors. Indeed, Du et al. (91,92), in a series of experiments in murine tubular epithelial cells, demonstrated the central role of caspase-8 in mediating apoptosis in response to exogenous nitric oxide or cytokine-induced nitric oxide synthesis. Furthermore, epithelial cell apoptosis could be blocked by caspase-8 inhibition using z-IETD-fmk or caspase-8 silencing with short hairpin RNA or through overexpression of the endogenous caspase-8 inhibitor cellular Flice-inhibitory protein, suggesting that caspase-8 inhibition may be an important target in ameliorating kidney injury in response to inflammation or ischemia-reperfusion; however, the complexity of the balance of factors involved in apoptosis and the response to sepsis were highlighted by the possibility that caspase inhibition may actually cause harm. Cauwels et al. (93) demonstrated that in a model of TNF-induced shock in mice, caspase inhibition was in fact associated with enhanced oxidative stress, mitochondrial damage, hyperacute hemodynamic collapse, kidney failure, and death. These authors found that there was a radical oxygen species–mediated pathway to lethal TNF-induced shock. Once caspase was inhibited, a caspase-dependent protective feedback on excessive radical oxygen species formation was removed, increasing lethality. These observations highlight how far we have to travel to understand the significance and complex biology of apoptosis in sepsis. Nonetheless, despite our limited understanding, some promising results have emerged from the use of an endogenous phospholipid growth factor (lysoosphosphatidic acid) with antiapoptotic properties. In a recent mouse model of ischemia/reperfusion, lysoosphosphatidic acid prevented tubular cell apoptosis, loss of brush border integrity, neutrophil influx, complement activation, and loss of renal function (94).

**Corticosteroids**

One of the most controversial areas of sepsis therapy is likely the use of exogenous corticosteroids. In a seminal article by Annane (95) in 2002, a 7-d treatment with low dosages of hydrocortisone and fluocortisone significantly reduced the risk for death in patients with septic shock and relative adrenal insufficiency. This benefit was achieved without increasing adverse events. The rationale is clear: Glucocorticoids display a wide spectrum of anti-inflammatory properties that have been identified through a host of experimental models and also exhibit profound effects on the cardiovascular system (96); however, the ability to demonstrate “relative adrenal insufficiency” in critically ill patients remains unclear, and preliminary results from the large, multicenter randomized Corticosteroid Therapy of Septic Shock (CORTICUS) trial were negative (97). This randomized, controlled study compared hydrocortisone with placebo use in septic shock and was suspended after enrolling roughly 500 patients with no difference in the overall 28-d mortality rate. Time to shock reversal did seem to be faster in the corticosteroid group. Whether the more rapid correction of shock results in less AKI is not yet available, and the full publication will be informative in this regard.

**Extracorporeal Blood Purification**

Extracorporeal blood purification (EBP) is a treatment in which a patient's blood is passed through a device (e.g., membrane, sorbent) where solute (e.g., waste products, toxins) and fluid are removed. EBP is primarily used in patients with renal failure (RRT). More than 20 yr ago, it was suggested that EBP could remove inflammatory mediators from the plasma of patients with sepsis and improve pulmonary function (98). Subsequently, surrogate clinical improvements with hemofiltration were reported in animal and human studies, and cytokine removal from the circulation of animals and humans with sepsis has been demonstrated (99,100). Shortly after, a survival benefit associated with higher dosages of continuous hemofiltration was reported (101). With these advances, EBP as a treatment for human septic shock was born. Since that time, many technological advances have occurred, along with substantial changes in our basic understanding of sepsis and the inflammatory response. Modifications of existing technologies and new approaches have created a vast array of possible therapies to use or investigate.

**Restoration of Immune Homeostasis**

The pathophysiology of sepsis is complex and not completely understood; however, it is generally accepted that circulating proinflammatory and anti-inflammatory mediators seem to participate in the complex cascade of events, which leads to cell and organ dysfunction and, in many cases, death. These soluble mediators include eicosanoids, leukotrienes, complement, cytokines, chemokines, coagulation factors, and other potentially important small peptides and vasogenic substances. Multiple unsuccessful attempts have been made to block the inflammatory response; however, recent successes in patients with severe sepsis have come from broad-spectrum immunomodulation, such as APC (84) and low-dosage corticosteroids (95,96), rather than specific blockers of inflammation. Moreover, growing evidence suggests that the anti-inflammatory response to sepsis induces immunoparalysis and may be just as dangerous or even more deleterious compared with the proinflammatory response. Thus, the goal of EBP should be to restore homeosta-
sism rather than to inhibit selectively pro- or anti-inflammatory mediators.

Most immune mediators are water-soluble and fall into the “middle molecular weight” category (approximately 5 to 50 kD) and hence can theoretically be removed by EBP (19). EBP technologies can remove these inflammatory mediators via convection, diffusion, or adsorption. The effects are broad spectrum, autoregulating, and limited to the circulating pool of inflammatory mediators rather than influencing local tissue concentrations. These advantages provide a powerful rationale for EBP in sepsis and sepsis-induced AKI.

Organ Support
Although the modulation of inflammatory mediators seems to be the major principle for blood purification in sepsis, this therapy may also offer additional physiologic benefits, including temperature control, acid-base control, fluid balance control, cardiac support, protective lung support, brain protection with preservation of cerebral perfusion, bone marrow protection, and blood detoxification and liver support. The extracorporeal circulation can be a potent modulator of body temperature and overall thermal balance. Negative thermal balance can be obtained depending on the length of blood lines, room temperature, and the replacement fluid temperature. Cardiac support can be achieved by the optimization of fluid balance, the reduction of organ edema, and the restoration of desirable levels of preload and afterload. By optimizing the patient’s volume state and offering the ability to remove interstitial fluid, extracorporeal therapy may provide additional support to the failing lung (102,103). Blood purification may improve the encephalopathy of sepsis by removing uremic toxins and amino acid derivatives and correcting acidemia. Continuous therapies offer the additional advantage of minimizing both osmotic shifts and hemodynamic insults that threaten cerebral perfusion pressure (104). Through the removal of uremic toxins, blood purification also reverses immunoparalysis (105) and may improve bone marrow function such as erythropoiesis (106).

Different Purification Technologies and Their Evaluation in Sepsis
EBP therapies that are designed to remove substances from the circulation now include hemodialysis (intermittent or continuous high flux), hemofiltration (high volume or high cutoff), plasma therapy, hemoadsorption, and combinations of any of these. In recent years, there have been considerable advances in our understanding and technical capability, but consensus on how and when to use these therapies remains elusive and the subject of ongoing research. Controversy exists as to whether continuous therapies have an advantage over intermittent hemodialysis in the management of AKI in intensive care (107), and a nonrandomized study recently found a higher relative risk for death for patients who were treated with continuous RRT (CRRT) compared with intermittent dialysis, even after adjustment for multiple risk factors (108). In a recent Cochrane review (107), no differences in mortality could be demonstrated between intermittent and continuous therapy, but the authors noted that many of the studies excluded patients with significant hypotension, and they did demonstrate that continuous therapies led to improved mean arterial pressure and less escalation of pressor support, leading the authors to conclude that CRRT may be the preferred mode of treatment in unstable patients. This is consistent with the recommendations of the Surviving Sepsis Campaign, which states that “in the absence of hemodynamic instability,” continuous and intermittent therapies are considered equivalent (26), noting, however, that intermittent therapies may be poorly tolerated in the most unstable patients such as those with severe septic shock. As a final note, it was demonstrated that standard intermittent hemodialysis has minimal to no impact on several important inflammatory cytokines (109); however, the use of hybrid therapies such as intermittent treatment with high-cutoff membranes (described next) or sustained low-efficiency dialysis (SLED) holds promise. SLED, for example, has been shown to provide excellent clearance of low molecular weight solutes, good tolerability in the critically ill, and reasonable clearance of somewhat larger molecules (110–112). Whether this therapy can modulate the immune system in sepsis remains to be demonstrated.

Continuous High-Flux Dialysis. High-flux membranes have a higher filtration rate than low-flux membranes for a given transmembrane pressure. They are also more permissive to the movement of middle molecules. As such, high-flux technologies may be of value as an immunomodulatory therapy. Continuous high-flux dialysis (CHFD) technology uses a highly permeable dialyzer with blood and dialysate flowing countercurrent. Ultrafiltrate produced in the proximal portion of the fibers is reinfused by backfiltration in the distal portion of the fibers so that replacement fluid is not required. It has mainly been developed to optimize the clearance of middle molecules without compromising the clearance of urea. Early studies have shown cytokine removal with CHFD, so the potential to exploit this therapy for sepsis certainly exists (113). Unfortunately, there are very limited data on the use of CHFD as a mode of EBP in human sepsis.

High-Volume Hemofiltration. Hemofiltration is achieved by convective clearance, in which solutes are transported along with movement of solvent in response to positive transmembrane pressure. Studies comparing convective and diffusive clearance have shown that middle molecular weight substances and large molecules are better removed by convection (114). Although most inflammatory mediator molecules fall in the middle molecular weight category, they have very high generation rates relative to uremic toxins; therefore, traditional effluent flow rates of 1 to 2 L/h have very little effect. Furthermore, both convection and adsorption are responsible for cytokine removal and depend on high flow rates and transmembrane pressure (99,100). It is generally agreed that conventional hemofiltration is not an effective modality for treatment of sepsis, as borne out in animal and human studies (115). Investigators hypothesized that higher hemofiltration rates would be necessary in sepsis, on the basis of encouraging animal and human studies (105,115). High-volume hemofiltration (HVHF), defined by a flow rate in excess of 35 ml/kg per
H and often as high as 75 to 120 ml/kg per h, may achieve clinically meaningful convective and adsorptive removal of inflammatory mediators. The possible importance of the former dosage was demonstrated in a single-center, randomized clinical trial by Ronco et al. (101), who found a significant benefit of two doses of HVHF on ICU mortality in patients with acute renal failure. In subgroup analysis focusing on patients with sepsis (11 to 14% of the total population enrolled), the patients who received the highest dosage experienced the lowest mortality. Of note, these patients required intervention for renal failure, and, as yet, published guidelines state that there is no evidence for therapies such as HVHF independent of the need for RRT (26).

In a nonrandomized study, Honore et al. (116) found that short-term, high-volume isovolemic hemofiltration (35 L over 4 h) led to hemodynamic improvement in slightly more than half of a group of patients with refractory septic shock. Despite these intriguing results, larger trials that examine HVHF as an adjunctive therapy in human sepsis are needed before such therapy can be routinely advocated.

Finally, it is difficult to determine whether the benefits of HVHF simply reflect increased solute removal or truly reflect greater convective clearance. In a landmark study of dialysis dosage in the ICU, Schiiff et al. (117) randomly assigned 160 patients with acute renal failure to daily or alternate-day intermittent hemodialysis and demonstrated a dramatic reduction in mortality from 46 to 28% (P = 0.01), with faster return of renal function at 9 versus 16 d (P = 0.001) in favor of the daily dialysis group. Patients with severe shock that required CRRT were excluded from this trial; however, approximately 32 to 41% of patients had sepsis as a cause of their renal failure, suggesting that daily intermittent therapy is an appropriate choice to minimize AKI in the more stable patient with septic AKI.

Hemoadsorption. Hemoadsorption is a technique whereby adsorbents, typically charcoal and resins, attract solutes through a variety of forces, including hydrophobic interactions, ionic (or electrostatic) attraction, hydrogen bonding, and van der Waals interactions. Selectivity can be achieved by manipulating the structure of solid-phase sorbents (118), for example by their size and ability of solutes to penetrate the porous network of the sorbent materials. Previously, poor biocompatibility was a limitation; however, newer resin sorbents have added a biocompatible outer layer. In addition, the adsorption characteristics make it possible to target high molecular weight molecules, exceeding the cutoff of synthetic high-flux dialysis membranes and making hemoadsorption an attractive strategy for intervention in sepsis. A recent systematic review by Cruz et al. (119) found that polymyxin-B hemoadsorption had favorable effects on mean arterial pressure, dopamine use, oxygenation, and mortality in sepsis; however, they cautioned that study quality and sample sizes were such that confirmation of these benefits is required in larger studies. Sorbents have been applied in combination with different treatment modalities, including coupled with hemodialysis or coupled with plasma filtration. The choice of modality is based on the properties of the sorbent and the technique used.

High Cutoff Hemofiltration or Hemodialysis. Another potentially useful strategy to increase mediator removal is by using high-cutoff (HCO) membranes, which are porous enough to achieve the removal of larger molecules (approximately 15 to 60 kD). Such EBP using HCO membranes in sepsis-related AKI has a widely accepted biologic rationale. Its ability to remove cytokines in ex vivo and in vivo studies has now been shown to be greater than that of any other technology so far (120) and has increased survival in experimental models of sepsis (121). HCO therapy seems to have beneficial effects on immune cell function (122), and preliminary human studies using intermittent hemodialysis with HCO membranes have confirmed its ability to remove marker cytokines IL-6 and IL-1 receptor antagonist, with a decreased dosage of norepinephrine in patients with sepsis (123). HCO membrane–based EBP has now been applied in at least four clinical studies and to the treatment of >70 patients with septic AKI with no reports of serious adverse effects. Predictably, albumin losses are significantly higher than that experienced during high-flux hemodialysis (7.7 versus <1.0 g per treatment) (124), but may be attenuated by using HCO membranes in a diffusive rather than convective manner while still preserving the effect on cytokine clearance. A phase II randomized, controlled trial is now under way for this promising therapy.

Plasma Therapy. The term “plasma therapy” actually encompasses two therapies: Plasmapheresis and plasma exchange. In plasmapheresis, plasma separated from blood cells flows along a column (or columns) that contains different adsorbents, after which the processed plasma is re-infused back to the patient. Plasma exchange is a single-step process in which blood is separated into plasma and cells and the cells are returned back to the patient while the plasma is replaced with either donor plasma or albumin. Replacing volume lost with fresh-frozen plasma is also done to replete any factor(s) needed to restore homeostasis or correct the underlying disorder for which the plasma therapy was prescribed. With respect to sepsis, it has been argued that plasma therapy is most likely to be effective in patients with sepsis-associated thrombotic microangiopathy (125). Recent animal studies and clinical trials showed plasma therapy to be a promising EBP technology in sepsis (126). An emerging hybrid technology called coupled plasma filtration adsorption uses an activated charcoal sorbent cartridge placed downstream from a plasma filter, improving the removal of nonspecific septic mediators with promising results in early small trials (127–129). Another kind of sorbent cartridge is an immunosorbent column with mono- or polyclonal antibody–coated resin through which filtered plasma is pumped. This setup is called coupled plasma filtration immunoabsorption, which could improve the removal of specific mediators. Clinical studies of these modalities are under way.

EBP Limitations and Future Innovations

Although the use of EBP in sepsis and sepsis-related AKI seems biologically plausible, with supportive animal research and a
dose-response study showing a survival benefit of HVHF, many questions still remain unanswered, including the timing, duration, intensity, and frequency of these therapies in the clinical settings. Current technologies are inadequate for the removal of middle molecules, and practice worldwide is extremely variable (130,131). Furthermore, there is lack of large-scale randomized clinical trials evaluating the efficacy of these therapies to improve valid clinical outcomes (mortality or organ failure), rather than surrogate markers such as mediator clearance or transient improvement in physiologic variables.

Finally, with the recognition that extracorporeal modalities cannot fully substitute the biologic functions of renal cells, investigators have developed a bioartificial kidney that consists of a renal tubule assist device that contains human proximal tubular cells connected in tandem with a continuous renal replacement circuit. Preliminary results suggest that this device may replace some of the metabolic, endocrine, and immunologic function in sepsis-associated AKI while potentially modifying its natural history (132,133). Results of a phase III trial that has stopped enrollment are not yet available.

Facilitating Renal Repair and Recovery

The final approach to sepsis-associated AKI is to concentrate on repair and recovery. This is logical because the vast majority of patients with sepsis likely already have some degree of renal injury at presentation even if functional markers such as creatinine and urine output are not yet abnormal. Thus, facilitating recovery may be the best option.

Because more than 80% of survivors of severe AKI, defined by need for RRT, will recover renal function before hospital discharge (130), the most important way to facilitate recovery is to keep the patient alive; however, emerging evidence has suggested that the mode of initial RRT may have a significant impact on the likelihood of subsequent renal recovery. Two separate studies, one from an international consortium (131) and one from a large national database in Sweden (134), found virtually identical results. Patients who were initially treated with intermittent hemodialysis had a significantly lower likelihood of recovery compared with those who were treated with CRRT, even after adjustment for baseline characteristics (odds ratio 2.6; 95% confidence interval 1.5 to 4.3). Furthermore, in the Swedish study, the effect was still detectable 7 yr after discharge. It should be noted that these studies were observational; therefore, causality cannot be attributed. Furthermore, in the meta-analyses of continuous versus intermittent therapies, renal recovery was not shown to be different between the two modalities (107,135). In the former analysis, when one study with significant baseline differences was excluded, the relative risk (1.66) for impaired renal recovery was numerically higher with intermittent dialysis; however, this did not reach statistical significance. Nonetheless, these observations provide rationale for ongoing, adequately powered, prospective, randomized studies.

The extent of recovery of renal function after AKI is an area that has not been well studied. In a review of this topic, Block and Schoolwerth (136) highlighted that although survival free of dialysis seems to be the most frequent outcome, a significant proportion of survivors have persistent, more advanced stages of chronic kidney disease, and, indeed, some of these will ultimately return to a state of permanent dialysis dependence. For this reason, strategies to improve not only the short term but also the long term prognosis in AKI are needed.

Pharmacology may provide an avenue for improving the chances of renal recovery. As already mentioned, molecules such as NGAL can promote renal tubule formation and might enhance tubule repair after AKI (60,61). A host of other compounds are now under evaluation for their potential regenerative and pro-proliferative effects. These compounds include growth factors and antiapoptotic substances. Numerous growth factors, including IGF, hepatocyte growth factor, and vascular endothelial growth factor, have important antiapoptotic and pro-proliferative effects, with promising results in animal studies (137–140). Unfortunately, early clinical trials have not yielded consistent results (141,142) and further studies are under way.

Finally, two agents, bone morphogenic protein-7 (BMP-7) and erythropoietin, currently in use for bone fractures and anemia, respectively, have promising, albeit largely hypothetical, effects on renal tubular cells. BMP-7 a member of the TGF-β superfamily of cytokines, is highly expressed in renal tubules and is thought to promote maintenance of epithelial phenotype. During the evolution of experimental diabetic nephropathy, renal expression of BMP-7 and its receptor declines, and it seems likely that loss of BMP-7 activity is profibrogenic in proximal tubular cells (143). Neutralization of endogenous BMP-7 in cultured proximal tubular cells raises the expression of fibronectin and increases collagen mRNA levels; therefore, it seems that BMP-7 is an attractive candidate as a pro-epithelial, antifibrosis agent for the kidney. Although currently in wide use for the treatment of anemia, erythropoietin also has important antiapoptotic effects that could have important consequences for the kidney. This has led many authors to speculate as to whether this drug could be of benefit in AKI (144). Clinical trials for both of these agents are urgently needed, although in light of recent evidence suggesting the potential for harm with erythropoietin vis-à-vis high hemoglobin targets in patients with chronic kidney disease, the use of this agent in advance of clinical trials needs careful consideration of the risks and benefits (145,146).

Conclusions

In this review, we have focused on five dynamic areas of research in sepsis-related AKI: Prevention, early recognition, pharmacologic intervention, EBP, and promotion of renal recovery. Emerging evidence supports the need for earlier interventions to recognize, treat, and/or prevent kidney dysfunction and injury before it becomes overtly manifest by rising creatinine and falling urine output. Advances in the clinical management of sepsis and nonrenal organ dysfunction may spill over favorably into the realm of AKI. The peak concentration hypothesis provides a rational paradigm for the use of existing, hybrid, and novel extracorporeal thera-
pies for the restoration of immune homeostasis, with exciting developments and ongoing clinical trials. Finally, the choice of renal replacement modality, as well as promising new mitogenic or antifibrotic therapies, may help to restore renal structure and function toward the premorbid baseline, minimizing the long-term sequelae that arise from permanent kidney damage in the context of sepsis-related AKI.

**Disclosures**

None.

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