

Potential Interventions in Sepsis-Related Acute Kidney Injury

Claudio Ronco,* John A. Kellum,[†] Rinaldo Bellomo,[‡] and Andrew A. House[§]

*Department of Nephrology, St. Bortolo Hospital, International Renal Research Institute Vicenza, Vicenza, Italy;

[†]Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania;

[‡]Department of Critical Care Medicine, Austin and Repatriation Medical Center, Melbourne, Australia; and [§]Division of Nephrology, London Health Sciences Centre, University Hospital, London, Ontario, Canada

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.

Clin J Am Soc Nephrol 3: 531-544, 2008. doi: 10.2215/CJN.03830907

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-

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Andrew A. House, Division of Nephrology, London Health Sciences Centre, University Hospital, 339 Windermere Road, London, Ontario, Canada N6A 5A5. Phone: 519-663-3167; Fax: 519-663-8808; E-mail: andrew.house@lhsc.on.ca

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 concen-

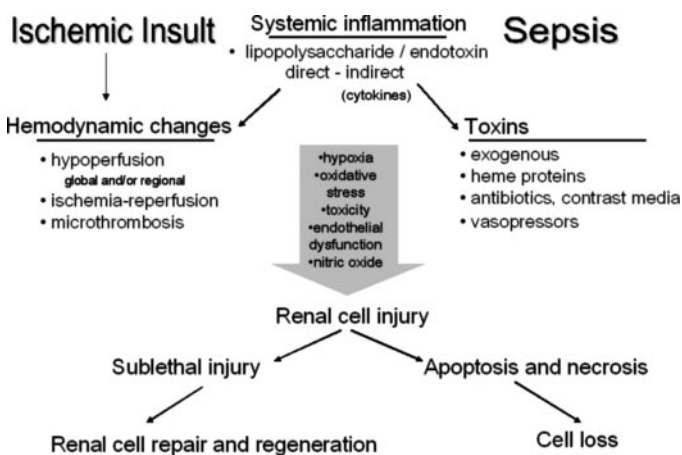


Figure 1. Pathogenic mechanisms of sepsis-related acute kidney injury.

tration 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 exhaus-

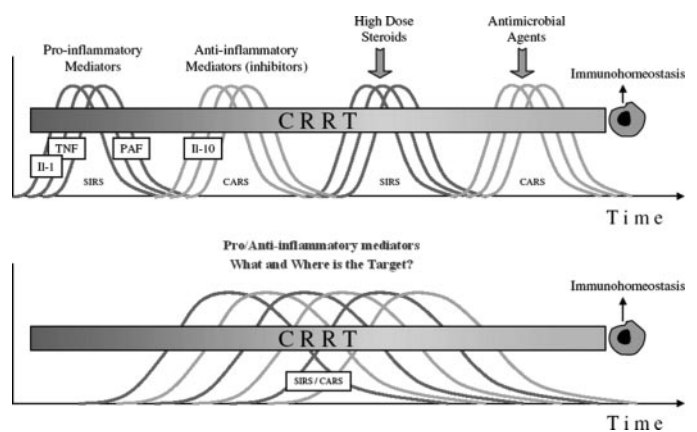


Figure 2. Peak concentration hypothesis. Peaks of mediators characteristic of systemic inflammatory response syndrome (SIRS) and compensated anti-inflammatory response syndrome (CARS) may be seen in sequence or in parallel. Broad-based control of peaks with continuous renal replacement therapy (CRRT) is hypothesized to lessen the degree of imbalance and restore immunohomeostasis. IL-1, interleukin-1; IL-10, interleukin-10; PAF, platelet-activating factor; TNF, tumor necrosis factor. Adapted from reference (19), with permission from Wiley-Blackwell Publishing, Ltd.

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 ≥ 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 $>70\%$ 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 starches 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 ≤ 90 mmHg to standard therapy *versus* protocol-driven maintenance of central venous pressure from 8 to 12 mmHg, mean arterial pressure ≥ 65 mmHg, and urine output ≥ 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 hyporesponsive to catecholamines (42). Furthermore, the presence of high levels of endogenous (and exogenous) catecholamines can lead to desensitization of adrenoreceptors. These observations, coupled with inappropriately 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 hemoxygenase-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 $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ 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. Nevier *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 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 (lysophosphatidic acid) with antiapoptotic properties. In a recent mouse model of ischemia/reperfusion, lysophosphatidic 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 fludrocortisone 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-

sis 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 counter-current. 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, Schiffel *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 immunoadsorption, 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-proliferate 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-proliferation 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.

References

- Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW: Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 16: 3365–3370, 2005
- Ahlstrom A, Kuitunen A, Peltonen S, Hynninen M, Tallgren M, Aaltonen J, Pettila V: Comparison of 2 acute renal failure severity scores to general scoring systems in the critically ill. *Am J Kidney Dis* 48: 262–268, 2006
- Kellum JA, Levin N, Bouman C, Lameire N: Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care* 8: 509–514, 2002
- Bellomo R, Kellum JA, Ronco C: Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. *Intensive Care Med* 33: 409–413, 2007
- Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C: An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 34: 1913–1917, 2006
- Bagshaw SM, George C, Dinu I, Bellomo R: A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* October 25, 2007 [epub ahead of print]
- Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit Care* 10: R73, 2006
- Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. *Chest* 101: 1644–1655, 1992
- Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R: Report of the American-European Consensus conference on acute respiratory distress syndrome: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. *J Crit Care* 9: 72–81, 1994
- Ricci Z, Cruz D, Ronco C: The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int* 2007, in press
- Molitoris BA, Levin A, Warnock DG, Joannidis M, Mehta RL, Kellum JA, Ronco C, Shah S, Acute Kidney Injury Network: Improving outcomes from acute kidney injury. *J Am Soc Nephrol* 18: 1992–1994, 2007
- Bellomo R, Wan L, May C: Managing septic acute renal failure: “Fill and spill”? “squeeze and diurese”? or “block Bax to the max”? *Crit Care Resusc* 6: 12–16, 2004
- Molitoris BA, Sandoval RM: Intravital multiphoton microscopy of dynamic renal processes. *Am J Physiol Renal Physiol* 288: F1084–F1089, 2005
- Wu L, Gokden N, Mayeux PR: Evidence for the role of reactive nitrogen species in polymicrobial sepsis-induced renal peritubular capillary dysfunction and tubular injury. *J Am Soc Nephrol* 18: 1807–1815, 2007
- Dagher PC, Herget-Rosenthal S, Ruehm SG, Jo SK, Star RA, Agarwal R, Molitoris BA: Newly developed techniques to study and diagnose acute renal failure. *J Am Soc Nephrol* 14: 2188–2198, 2003
- Molitoris BA: Transitioning to therapy in ischemic acute renal failure. *J Am Soc Nephrol* 14: 265–267, 2003
- Molitoris BA, Sutton TA: Endothelial injury and dysfunction: Role in the extension phase of acute renal failure. *Kidney Int* 66: 496–499, 2004
- Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 348: 138–150, 2003
- Ronco C, Tetta C, Mariano F, Wratten ML, Bonello M, Bordoni V, Cardona X, Inguaggiato P, Pilotto L, d’Intini V, Bellomo R: Interpreting the mechanisms of continuous renal replacement therapy in sepsis: The peak concentration hypothesis. *Artif Organs* 27: 792–801, 2003
- Yasuda H, Yuen PS, Hu X, Zhou H, Star RA: Simvastatin improves sepsis-induced mortality and acute kidney injury via renal vascular effects. *Kidney Int* 69: 1535–1542, 2006
- Chen HW, Kuo HT, Chai CY, Ou JL, Yang RC: Pretreatment of curcumin attenuates coagulopathy and renal injury in LPS-induced endotoxemia. *J Endotoxin Res* 13: 15–23, 2007
- Gupta A, Rhodes GJ, Berg DT, Gerlitz B, Molitoris BA, Grinnell BW: Activated protein C ameliorates LPS-induced acute kidney injury and downregulates renal iNOS and angiotensin 2. *Am J Physiol Renal Physiol* 293: F245–F254, 2007
- Molitoris BA: Renal blood flow in sepsis: a complex issue. *Crit Care* 9: 327–328, 2005
- Langenberg C, Bellomo R, May CN, Egi M, Wan L, Morgner S: Renal vascular resistance in sepsis. *Nephron Physiol* 104: 1–11, 2006
- Langenberg C, Wan L, Egi M, May CN, Bellomo R: Renal blood flow and function during recovery from experimental septic acute kidney injury. *Intensive Care Med* 33: 1614–1618, 2007
- Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM, Surviving Sepsis Campaign Management Guidelines Committee: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 32: 858–873, 2004
- Russell JA: Management of sepsis. *N Engl J Med* 355: 1699–1713, 2006
- Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345: 1368–1377, 2001
- Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R: A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO₂ Collaborative Group. *N Engl J Med* 333: 1025–1032, 1995

30. Michard F: Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 103: 419–428, quiz 449–445, 2005
31. Van Biesen W, Yegenaga I, Vanholder R, Verbeke F, Hoste E, Colardyn F, Lameire N: Relationship between fluid status and its management on acute renal failure (ARF) in intensive care unit (ICU) patients with sepsis: a prospective analysis. *J Nephrol* 18: 54–60, 2005
32. Bagshaw SM, Bellomo R: Fluid resuscitation and the septic kidney. *Curr Opin Crit Care* 12: 527–530, 2006
33. Davidson IJ: Renal impact of fluid management with colloids: A comparative review. *Eur J Anaesthesiol* 23: 721–738, 2006
34. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L: Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: A multicentre randomised study. *Lancet* 357: 911–916, 2001
35. Davidson IJ: Deleterious renal effects of hydroxyethyl starch 130/0.4 and 200/0.5 solutions. *Eur J Anaesthesiol* 24: 892–893, 2007
36. Boldt J: Renal impact of fluid management with colloids. *Eur J Anaesthesiol* 24: 891–892, 2007
37. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 350: 2247–2256, 2004
38. Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP: A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: A randomized controlled trial. *Shock* 26: 551–557, 2006
39. Rivers EP, Kruse JA, Jacobsen G, Shah K, Loomba M, Otero R, Childs EW: The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. *Crit Care Med* 35: 2016–2024, 2007
40. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, Connors AF, Jr, Hite RD, Harabin AL: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 354: 2213–2224, 2006
41. Di Giandomenico D, Morimatsu H, May CN, Bellomo R: Increasing renal blood flow: low-dose dopamine or medium-dose norepinephrine. *Chest* 125: 2260–2267, 2004
42. Barrett LK, Singer M, Clapp LH: Vasopressin: Mechanisms of action on the vasculature in health and in septic shock. *Crit Care Med* 35: 33–40, 2007
43. Russell JA: Vasopressin in vasodilatory and septic shock. *Curr Opin Crit Care* 13: 383–391, 2007
44. Patel BM, Chittock DR, Russell JA, Walley KR: Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 96: 576–582, 2002
45. Russell JA, Walley KR, Singer J, Gordon AC, Hebert P, Cooper J, Mehta S, Granton J, Holmes Boulton CL, Storms MM, Cook D, Presneill JJ, the VASST Investigators: A randomized controlled trial of low dose vasopressin versus norepinephrine infusion in patients who have septic shock. American Thoracic Society Annual International Conference, San Francisco, CA, May 18 through 23, 2007, A508
46. Burch JM, Moore EE, Moore FA, Franciose R: The abdominal compartment syndrome. *Surg Clin North Am* 76: 833–842, 1996
47. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345: 1359–1367, 2001
48. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: Intensive insulin therapy in the medical ICU. *N Engl J Med* 354: 449–461, 2006
49. Allen DA, Harwood S, Varagunam M, Raftery MJ, Yaqoob MM: High glucose-induced oxidative stress causes apoptosis in proximal tubular epithelial cells and is mediated by multiple caspases. *FASEB J* 17: 908–910, 2003
50. Augustin R, Pocar P, Wrenzycki C, Niemann H, Fischer B: Mitogenic and anti-apoptotic activity of insulin on bovine embryos produced in vitro. *Reproduction* 126: 91–99, 2003
51. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S: Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: Evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 86: 3257–3265, 2001
52. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G: Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab* 88: 1082–1088, 2003
53. Bellomo R, Egi M: Glycemic control in the intensive care unit: Why we should wait for NICE-SUGAR. *Mayo Clin Proc* 80: 1546–1548, 2005
54. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342: 1301–1308, 2000
55. Imai Y, Parodo J, Kajikawa O, de Perrot M, Fischer S, Edwards V, Cutz E, Liu M, Keshavjee S, Martin TR, Marshall JC, Ranieri VM, Slutsky AS: Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 289: 2104–2112, 2003
56. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Jr, Hite RD, Harabin AL: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 354: 2564–2575, 2006
57. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, MacKinnon RW, Li L, Balakrishnan VS, Pereira BJ, Bonventre JV, Jaber BL: Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. *J Am Soc Nephrol* 18: 904–912, 2007
58. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P: Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am Soc Nephrol* 14: 2534–2543, 2003
59. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P: Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 365: 1231–1238, 2005
60. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J,

- Schmidt-Ott KM, Chen X, Li JY, Weiss S, Mishra J, Cheema FH, Markowitz G, Suganami T, Sawai K, Mukoyama M, Kunis C, D'Agati V, Devarajan P, Barasch J: Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 115: 610–621, 2005
61. Mishra J, Mori K, Ma Q, Kelly C, Yang J, Mitsnefes M, Barasch J, Devarajan P: Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol* 15: 3073–3082, 2004
62. Sward K, Valsson F, Sellgren J, Ricksten SE: Bedside estimation of absolute renal blood flow and glomerular filtration rate in the intensive care unit: A validation of two independent methods. *Intensive Care Med* 30: 1776–1782, 2004
63. Erley CM, Bader BD, Berger ED, Vochazer A, Jorzik JJ, Dietz K, Risler T: Plasma clearance of iodine contrast media as a measure of glomerular filtration rate in critically ill patients. *Crit Care Med* 29: 1544–1550, 2001
64. Rabito CA, Panico F, Rubin R, Tolkoff-Rubin N, Teplick R: Noninvasive, real-time monitoring of renal function during critical care. *J Am Soc Nephrol* 4: 1421–1428, 1994
65. Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, Janssen O, Philipp T, Kribben A: Early detection of acute renal failure by serum cystatin C. *Kidney Int* 66: 1115–1122, 2004
66. Villa P, Jimenez M, Soriano MC, Manzanares J, Casasnovas P: Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients. *Crit Care* 9: R139–R143, 2005
67. Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Nacedo E, Gibney N, Tolwani A, Ronco C, Kellum JA, Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators: Diuretics and mortality in acute renal failure. *Crit Care Med* 32: 1669–1677, 2004
68. Mehta RL, Pascual MT, Soroko S, Chertow GM, PICARD Study Group: Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 288: 2547–2553, 2002
69. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL, High-Dose Furosemide in Acute Renal Failure Study Group: High-dose furosemide for established ARF: A prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Am J Kidney Dis* 44: 402–409, 2004
70. De Torrente A, Miller PD, Cronin RE, Paulsin PE, Erickson AL, Schrier RW: Effects of furosemide and acetylcholine in norepinephrine-induced acute renal failure. *Am J Physiol* 235: F131–F136, 1978
71. Kramer HJ, Schuurmann J, Wassermann C, Dusing R: Prostaglandin-independent protection by furosemide from oliguric ischemic renal failure in conscious rats. *Kidney Int* 17: 455–464, 1980
72. Karayannopoulos S: Letter: High-dose frusemide in renal failure. *BMJ* 2: 278–279, 1974
73. Cantarovich F, Fernandez JC, Locatelli A, Perez Loreda J: Furosemide in high doses in the treatment of acute renal failure. *Postgrad Med J* 47[Suppl]: 13–17, 1971
74. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, Fermanian J: Furosemide in acute oliguric renal failure: A controlled trial. *Nephron* 17: 51–58, 1976
75. Shilliday IR, Quinn KJ, Allison ME: Loop diuretics in the management of acute renal failure: A prospective, double-blind, placebo-controlled, randomized study. *Nephrol Dial Transplant* 12: 2592–2596, 1997
76. Vargas Hein O, Staegemann M, Wagner D, von Heymann C, Martin M, Morgera S, Spies C: Torsemide versus furosemide after continuous renal replacement therapy due to acute renal failure in cardiac surgery patients. *Ren Fail* 27: 385–392, 2005
77. Kellum JA: The use of diuretics and dopamine in acute renal failure: A systematic review of the evidence. *Crit Care* 1: 53–59, 1997
78. Lameire N, Vanholder R, Van Biesen W: Loop diuretics for patients with acute renal failure: helpful or harmful? *JAMA* 288: 2599–2601, 2002
79. Noble DW: Acute renal failure and diuretics: Propensity, equipoise, and the need for a clinical trial. *Crit Care Med* 32: 1794–1795, 2004
80. Schetz M: Should we use diuretics in acute renal failure? *Best Pract Res Clin Anaesthesiol* 18: 75–89, 2004
81. Kellum JA, M Decker J: Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 29: 1526–1531, 2001
82. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 356: 2139–2143, 2000
83. Morelli A, Ricci Z, Bellomo R, Ronco C, Rocco M, Conti G, De Gaetano A, Picchini U, Orecchioni A, Portieri M, Coluzzi F, Porzi P, Serio P, Bruno A, Pietropaoli P: Prophylactic fenoldopam for renal protection in sepsis: A randomized, double-blind, placebo-controlled pilot trial. *Crit Care Med* 33: 2451–2456, 2005
84. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ, Jr, Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 344: 699–709, 2001
85. Joyce DE, Gelbert L, Ciaccia A, DeHoff B, Grinnell BW: Gene expression profile of antithrombotic protein c defines new mechanisms modulating inflammation and apoptosis. *J Biol Chem* 276: 11199–11203, 2001
86. Cheng T, Liu D, Griffin JH, Fernandez JA, Castellino F, Rosen ED, Fukudome K, Zlokovic BV: Activated protein C blocks p53-mediated apoptosis in ischemic human brain endothelium and is neuroprotective. *Nat Med* 9: 338–342, 2003
87. Eichacker PQ, Danner RL, Suffredini AF, Cui X, Natanson C: Reassessing recombinant human activated protein C for sepsis: Time for a new randomized controlled trial. *Crit Care Med* 33: 2426–2428, 2005
88. Eichacker PQ, Natanson C: Increasing evidence that the risks of rhAPC may outweigh its benefits. *Intensive Care Med* 33: 396–399, 2007
89. Fauvel H, Marchetti P, Chopin C, Formstecher P, Neviere R: Differential effects of caspase inhibitors on endotoxin-induced myocardial dysfunction and heart apoptosis. *Am J Physiol Heart Circ Physiol* 280: H1608–H1614, 2001
90. Neviere R, Fauvel H, Chopin C, Formstecher P, Marchetti P: Caspase inhibition prevents cardiac dysfunction and

- heart apoptosis in a rat model of sepsis. *Am J Respir Crit Care Med* 163: 218–225, 2001
91. Du C, Guan Q, Diao H, Yin Z, Jevnikar AM: Nitric oxide induces apoptosis in renal tubular epithelial cells through activation of caspase-8. *Am J Physiol Renal Physiol* 290: F1044–F1054, 2006
 92. Du C, Guan Q, Yin Z, Zhong R, Jevnikar AM: IL-2-mediated apoptosis of kidney tubular epithelial cells is regulated by the caspase-8 inhibitor c-FLIP. *Kidney Int* 67: 1397–1409, 2005
 93. Cauwels A, Janssen B, Waeytens A, Cuvelier C, Brouckaert P: Caspase inhibition causes hyperacute tumor necrosis factor-induced shock via oxidative stress and phospholipase A2. *Nat Immunol* 4: 387–393, 2003
 94. de Vries B, Matthijsen RA, van Bijnen AA, Wolfs TG, Buurman WA: Lysophosphatidic acid prevents renal ischemia-reperfusion injury by inhibition of apoptosis and complement activation. *Am J Pathol* 163: 47–56, 2003
 95. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 288: 862–871, 2002
 96. Annane D, Cavaillon JM: Corticosteroids in sepsis: From bench to bedside? *Shock* 20: 197–207, 2003
 97. Sprung CL, Annane D, Briegel J, Keh D, Moreno R, Singer M, Weiss Y, Sorenson F: Corticosteroid therapy of septic shock (CORTICUS). American Thoracic Society Annual International Conference, San Francisco, CA, May 18 through 23, 2007, A507
 98. Gotloib L, Barzilay E, Shustak A, Lev A: Sequential hemofiltration in nonoliguric high capillary permeability pulmonary edema of severe sepsis: Preliminary report. *Crit Care Med* 12: 997–1000, 1984
 99. De Vriese AS, Colardyn FA, Philippe JJ, Vanholder RC, De Sutter JH, Lameire NH: Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol* 10: 846–853, 1999
 100. De Vriese AS, Vanholder RC, Pascual M, Lameire NH, Colardyn FA: Can inflammatory cytokines be removed efficiently by continuous renal replacement therapies? *Intensive Care Med* 25: 903–910, 1999
 101. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 356: 26–30, 2000
 102. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA, UNLOAD Trial Investigators: Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 49: 675–683, 2007
 103. Huang H, Yao T, Wang W, Zhu D, Zhang W, Chen H, Fu W: Continuous ultrafiltration attenuates the pulmonary injury that follows open heart surgery with cardiopulmonary bypass. *Ann Thorac Surg* 76: 136–140, 2003
 104. Davenport A: Renal replacement therapy in the patient with acute brain injury. *Am J Kidney Dis* 37: 457–466, 2001
 105. Yekebas EF, Eisenberger CF, Ohnesorge H, Saalmuller A, Elsner HA, Engelhardt M, Gillesen A, Meins J, The M, Strate T, Busch C, Knoefel WT, Bloechle C, Izbicki JR: Attenuation of sepsis-related immunoparalysis by continuous veno-venous hemofiltration in experimental porcine pancreatitis. *Crit Care Med* 29: 1423–1430, 2001
 106. Righetti M, Ferrario GM, Milani S, Serbelloni P, Sessa A: A single centre study about the effects of HFR on anemia. *G Ital Nefrol* 21[Suppl 30]: S168–S171, 2004
 107. Rabindranath K, Adams J, Macleod A, Muirhead N: Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *Cochrane Database Syst Rev* (3): CD003773, 2007
 108. Cho KC, Himmelfarb J, Paganini E, Ikizler TA, Soroko SH, Mehta RL, Chertow GM: Survival by dialysis modality in critically ill patients with acute kidney injury. *J Am Soc Nephrol* 17: 3132–3138, 2006
 109. Tarakcioglu M, Erbagci AB, Usalan C, Devenci R, Kocabas R: Acute effect of hemodialysis on serum levels of the proinflammatory cytokines. *Mediators Inflamm* 12: 15–19, 2003
 110. Fiaccadori E, Maggiore U, Parenti E, Giacosa R, Picetti E, Rotelli C, Tagliavini D, Cabassi A: Sustained low-efficiency dialysis (SLED) with prostacyclin in critically ill patients with acute renal failure. *Nephrol Dial Transplant* 22: 529–537, 2007
 111. Marshall MR, Golper TA, Shaver MJ, Alam MG, Chatoth DK: Urea kinetics during sustained low-efficiency dialysis in critically ill patients requiring renal replacement therapy. *Am J Kidney Dis* 39: 556–570, 2002
 112. Van Biesen W, Veys N, Vanholder R: Intermittent hemodialysis for renal replacement therapy in intensive care: new evidence for old truths. *Contrib Nephrol* 156: 304–308, 2007
 113. Lonnemann G, Bechstein M, Linnenweber S, Burg M, Koch KM: Tumor necrosis factor-alpha during continuous high-flux hemodialysis in sepsis with acute renal failure. *Kidney Int Suppl* (72): S84–S87, 1999
 114. Brunet S, Leblanc M, Geadah D, Parent D, Courteau S, Cardinal J: Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. *Am J Kidney Dis* 34: 486–492, 1999
 115. Bouman CS, Oudemans-van Straaten HM, Schultz MJ, Vroom MB: Hemofiltration in sepsis and systemic inflammatory response syndrome: The role of dosing and timing. *J Crit Care* 22: 1–12, 2007
 116. Honore PM, Jamez J, Wauthier M, Lee PA, Dugernier T, Pirenne B, Hanique G, Matson JR: Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit Care Med* 28: 3581–3587, 2000
 117. Schiffl H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 346: 305–310, 2002
 118. Cruz DN, Bellomo R, Ronco C: Clinical effects of polymyxin B-immobilized fiber column in septic patients. *Contrib Nephrol* 156: 444–451, 2007
 119. Cruz DN, Perazella MA, Bellomo R, de Cal M, Polanco N, Corradi V, Lentini P, Nalesso F, Ueno T, Ranieri VM, Ronco C: Effectiveness of polymyxin B-immobilized fiber column in sepsis: A systematic review. *Crit Care* 11: R47, 2007

120. Uchino S, Bellomo R, Goldsmith D, Davenport P, Cole L, Baldwin I, Panagiotopoulos S, Tipping P: Super high flux-hemofiltration: A new technique for cytokine removal. *Intensive Care Med* 28: 651-655, 2002
121. Lee PA, Weger GW, Pryor RW, Matson JR: Effects of filter pore size on efficacy of continuous arteriovenous hemofiltration therapy for *Staphylococcus aureus*-induced septicemia in immature swine. *Crit Care Med* 26: 730-737, 1998
122. Morgera S, Haase M, Rocktaschel J, Bohler T, von Heymann C, Vargas-Hein O, Krausch D, Zuckermann-Becker H, Muller JM, Kox WJ, Neumayer HH: High permeability haemofiltration improves peripheral blood mononuclear cell proliferation in septic patients with acute renal failure. *Nephrol Dial Transplant* 18: 2570-2576, 2003
123. Morgera S, Haase M, Kuss T, Vargas-Hein O, Zuckermann-Becker H, Melzer C, Krieg H, Wegner B, Bellomo R, Neumayer HH: Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. *Crit Care Med* 34: 2099-2104, 2006
124. Haase M, Bellomo R, Baldwin I, Haase-Fielitz A, Fealy N, Davenport P, Morgera S, Goehl H, Storr M, Boyce N, Neumayer HH: Hemodialysis membrane with a high-molecular-weight cutoff and cytokine levels in sepsis complicated by acute renal failure: A phase 1 randomized trial. *Am J Kidney Dis* 50: 296-304, 2007
125. Peng ZY, Kiss JE, Cortese-Hasset A, Carcillo JA, Nguyen TC, Kellum JA: Plasma filtration on mediators of thrombotic microangiopathy: An in vitro study. *Int J Artif Organs* 30: 401-406, 2007
126. Bengsch S, Boos KS, Nagel D, Seidel D, Inthorn D: Extracorporeal plasma treatment for the removal of endotoxin in patients with sepsis: Clinical results of a pilot study. *Shock* 23: 494-500, 2005
127. Formica M, Inguaggiato P, Bainotti S, Wratten ML: Coupled plasma filtration adsorption. *Contrib Nephrol* 156: 405-410, 2007
128. Bellomo R, Tetta C, Ronco C: Coupled plasma filtration adsorption. *Intensive Care Med* 29: 1222-1228, 2003
129. Ronco C, Brendolan A, Lonnemann G, Bellomo R, Piccinni P, Digito A, Dan M, Irone M, La Greca G, Inguaggiato P, Maggiore U, De Nitti C, Wratten ML, Ricci Z, Tetta C: A pilot study of coupled plasma filtration with adsorption in septic shock. *Crit Care Med* 30: 1250-1255, 2002
130. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten H, Ronco C, Kellum JA: Continuous renal replacement therapy: A worldwide practice survey—The Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators. *Intensive Care Med* 33: 1563-1570, 2007
131. Uchino S, Bellomo R, Kellum JA, Morimatsu H, Morgera S, Schetz MR, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-Van Straaten HM, Ronco C, Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators Writing Committee: Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. *Int J Artif Organs* 30: 281-292, 2007
132. Humes HD, Weitzel WF, Bartlett RH, Swaniker FC, Paganini EP, Luderer JR, Sobota J: Initial clinical results of the bioartificial kidney containing human cells in ICU patients with acute renal failure. *Kidney Int* 66: 1578-1588, 2004
133. Issa N, Messer J, Paganini EP: Renal assist device and treatment of sepsis-induced acute kidney injury in intensive care units. *Contrib Nephrol* 156: 419-427, 2007
134. Bell M, SWING, Granath F, Schon S, Ekblom A, Martling CR: Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. *Intensive Care Med* 33: 773-780, 2007
135. Tonelli M, Manns B, Feller-Kopman D: Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. *Am J Kidney Dis* 40: 875-885, 2002
136. Block CA, Schoolwerth AC: The epidemiology and outcome of acute renal failure and the impact on chronic kidney disease. *Semin Dial* 19: 450-454, 2006
137. Miller SB, Martin DR, Kissane J, Hammerman MR: Insulin-like growth factor I accelerates recovery from ischemic acute tubular necrosis in the rat. *Proc Natl Acad Sci U S A* 89: 11876-11880, 1992
138. Friedlaender M, Popovtzer MM, Weiss O, Nefesh I, Kopolovic J, Raz I: Insulin-like growth factor-1 (IGF-1) enhances recovery from HgCl₂-induced acute renal failure: the effects on renal IGF-1, IGF-1 receptor, and IGF-binding protein-1 mRNA. *J Am Soc Nephrol* 5: 1782-1791, 1995
139. Vijayan A, Martin DR, Sadow JL, Kissane J, Miller SB: Hepatocyte growth factor inhibits apoptosis after ischemic renal injury in rats. *Am J Kidney Dis* 38: 274-278, 2001
140. Kanellis J, Fraser S, Katerelos M, Power DA: Vascular endothelial growth factor is a survival factor for renal tubular epithelial cells. *Am J Physiol Renal Physiol* 278: F905-F915, 2000
141. Hirschberg R, Kopple J, Lipsett P, Benjamin E, Minei J, Albertson T, Munger M, Metzler M, Zaloga G, Murray M, Lowry S, Conger J, McKeown W, O'shea M, Baughman R, Wood K, Haupt M, Kaiser R, Simms H, Warnock D, Summer W, Hintz R, Myers B, Haentfling K, Capra W: Multi-center clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure. *Kidney Int* 55: 2423-2432, 1999
142. Venkataraman R, Kellum JA: Novel approaches to the treatment of acute renal failure. *Expert Opin Investig Drugs* 12: 1353-1366, 2003
143. Wang SN, Lapage J, Hirschberg R: Loss of tubular bone morphogenetic protein-7 in diabetic nephropathy. *J Am Soc Nephrol* 12: 2392-2399, 2001
144. Westenfelder C: Unexpected renal actions of erythropoietin. *Exp Nephrol* 10: 294-298, 2002
145. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A, CREATE Investigators: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 355: 2071-2084, 2006
146. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 355: 2085-2098, 2006