Sepsis and Acute Kidney Injury
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ABSTRACT
Sepsis is a severe and dysregulated inflammatory response to infection characterized by end-organ dysfunction distant from the primary site of infection. Development of acute kidney injury (AKI) during sepsis increases patient morbidity, predicts higher mortality, has a significant effect on multiple organ functions, is associated with an increased length of stay in the intensive care unit, and hence consumes considerable healthcare resources. When compared with AKI of non-septic origin, septic AKI is characterized by a distinct pathophysiology and therefore requires a different approach. Despite impressive advances in several fields of medicine, the pathophysiology, diagnostic procedures, and appropriate therapeutic interventions in sepsis are still highly debatable. Numerous immunomodulatory agents showing promise in preclinical studies fail to reduce the overwhelmingly high mortality rate of sepsis and provoke AKI when compared with other critically ill patients. Major impediments to progress in understanding, early diagnosis, and application of appropriate therapeutic modalities in sepsis-induced AKI include limited histopathologic information, few animal models that closely mimic human sepsis, and a relative shortage of specific diagnostic tools. Here we discuss the most recent advances in understanding the fundamental mechanisms of sepsis-induced AKI, characteristics of relevant animal models available, and potential therapies.


Sepsis is a serious medical condition characterized by a whole-body inflammatory state (systemic inflammatory-response syndrome) and the presence of a known or suspected infection that has severe consequences, including multiple organ failure.1 The clinical diagnosis of sepsis requires finding a focus of infection as well as at least two signs of systemic inflammatory-response syndrome that comprise abnormal body temperature (higher than 38°C or less than 36°C), heart rate >90 beats/min, respiration >20 breaths/min or arterial partial pressure of CO₂ <32 mmHg, and deranged white blood cell counts (greater than 12 × 10³/mm³, less than 4 × 10³/mm³, or greater than 10% bands).1-2 Except for the discovery of antimicrobial agents in the mid-1900s, little progress has been made in the management of sepsis, which remains a particularly serious problem for patients with ESRD.3 In fact, there are approximately one million reported cases and more than 200,000 deaths each year attributable to sepsis in the United States alone.4 This is a significant burden on health resources, with costs exceeding $10 billion per year in the United States.5,6

Acute kidney injury (AKI) is a frequent and serious complication of sepsis in intensive care unit (ICU) patients,7 particularly in the elderly.8 Moreover, there is strong evidence that sepsis and septic shock are the most important causes of AKI in critically ill patients, account for 50% or more of cases of AKI in ICUs, and associate with a very high mortality.9 Furthermore, there is evidence that even less severely ill patients with infection (patients with nonsevere pneumonia) have a significantly higher incidence of AKI and increased immune responses.10 Although septic shock is a leading cause of AKI, the underlying mechanisms are not completely known. Despite extensive research and progress in several other fields, the incidence, as well as mortality of septic AKI, remains unacceptably high.11 Perhaps an important factor in this dilemma is the relative lack of histopathologic information and reliance on creatinine measurements for assessment of kidney function.

Pathogenesis of Sepsis-induced AKI
Sepsis develops when the initial, appropriate host response to an infection becomes amplified and then dysregulated. Because of very high mortality rates, it is fundamental to promptly recognize sepsis-induced AKI and to choose the most appropriate therapeutic modality. This task, however, is still far from certain because of a lack of general consensus and conflicting data. It is well established that...

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the kidney is a commonly affected organ during sepsis, and its involvement carries a high risk of mortality.12,13 The pathophysiology of AKI in sepsis is complex and multi-factorial and includes intrarenal hemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells in the renal parenchyma, intraglomerular thrombosis, and obstruction of tubules with necrotic cells and debris (Figure 1).14 A growing body of evidence now suggests that the sepsis-induced immune responses involve the activation, in a sequential manner, of both pro- and anti-inflammatory mechanisms.15,16

After initial host-microbial interactions, there is widespread activation of the innate immune response, which coordinates a defensive response involving both humoral and cellular components.17 This in turn leads to secretion of various cytokines, most importantly IL-1,18 TNF-α,19 and IL-6,20 that progress to a state of cytokine storm, hemodynamic instability, and eventually organ dysfunction and septic shock. The precise nature of such hemodynamic instability and its consequence on renal blood flow (RBF) will be discussed in more detail below. This pro-inflammatory phase is followed by a compensatory anti-inflammatory immune response, an immunosuppressed state characterized by altered cytokine production and antigen presentation by monocytes, decreased lymphocyte proliferation, and increased apoptosis. It must be noted that these stages can overlap temporally.21

Several pro-inflammatory cytokines contribute to the development of sepsis, and others may be identifiable from other kinds of genetic screens.22 For instance, administration of recombinant IL-1 or TNF-α induces many of the features observed after lipopolysaccharide exposure or sepsis itself.18,19 Furthermore, anti-TNF monoclonal antibodies have beneficial effects in several animal models of sepsis.23 Nonetheless, these and other cytokine-blocking experiments have not been conclusive and have also failed in clinical trials.24 Recent preclinical studies suggest an anti-inflammatory role for soluble thrombomodulin in AKI,25 and release of stem cell factor by MMP-9 has an antiapoptotic effect through activation of cKit.26

Toll-like receptors (TLRs) are a class of proteins that play an important role in alerting the innate immune system.27,28 They are single membrane-spanning noncatalytic receptors that recognize structurally conserved molecules derived from invading pathogens. TLR-4 appears to play a key inflammatory role in AKI.29 There is a significant up-regulation of monocytes TLR-2 and TLR-4 expression in septic patients when compared with healthy individuals.30,31 In addition, the expression of TLR-2 and TLR-4 in hepatic and splenic macrophages is significantly increased in mice with experimental peritonitis induced by cecal ligation and puncture.31,32 These and other findings suggest that modulation of TLRs may become a novel therapeutic target especially in the treatment of organ injury accompanying sepsis. Although this is an interesting approach, it is imperative to note that apart from TLR modulation, sepsis also affects several other pathways including injury caused by endotoxin, complement cascade, coagulation pathway activation, release of arachidonic acid and nitric oxide, vascular injury, and others that mediate the development and course of sepsis. Such complexity may have been an important contributor to the failure of clinical trials targeting just one of these pathways.

**Biomarkers in Sepsis-induced AKI**

When compared with AKI of nonseptic origin, septic AKI is characterized by a distinct pathophysiology,14,33,34 and therefore important differences exist in patient characteristics, response to interventions, and clinical outcomes. This may also extend to unique patterns of plasma and urinary biomarkers in septic AKI. For instance, the excretion of IL-18 is higher in septic AKI than in nonseptic AKI.35,36 Moreover, an increased level of IL-18 predicts deteriorating kidney function approximately 24 to 48 hours before clinically significant AKI. AKI can be diagnosed by small changes in serum creatinine or acute reductions in urine output.38 Nevertheless, rising creatinine and oliguria during sepsis often appear after the window of opportunity for effective therapy has already passed. Moreover, sepsis decreases production of creatinine without major alterations in

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**Figure 1.** Key pathogenic pathways involved in the clinical course of sepsis that also have implications in the pathophysiology of sepsis-induced acute kidney injury.
body weight, hematocrit, or extracellular fluid and creates further limitations on using changes in creatinine levels as a reliable marker of AKI. Hence, it is essential to have markers that enable early detection. Molecules such as kidney injury molecule-1 or neutrophil gelatinase-associated lipocalin demonstrate exciting potential for this reason. Table 1 summarizes a partial list of emerging biomarkers that are in various phases of validation in AKI.

A recent study demonstrated that septic AKI patients have higher detectable plasma and urine neutrophil gelatinase-associated lipocalin compared with non-septic AKI patients. The utility of these and other novel biomarkers including cystatin C, liver fatty acid–binding protein, and netrin-1 for early detection of sepsis-induced AKI is very encouraging and may have prognostic as well as pathogenetic implications. For instance, urinary liver fatty acid–binding protein is significantly higher in AKI than non-AKI in adult ICU patients. On the other hand, netrin-1, a laminin-like protein with possible roles in neovascularization, cell adhesion, and tumorigenesis, is excreted in the urine as early as 1 hour after injury reaching approximately 30-fold increase by 3 hours and peaking at 6 hours after the insult. This window of opportunity to implement potential therapeutic interventions is indeed well before any detectable changes in blood urea nitrogen and serum creatinine would occur. The utility of such biomarkers may be of particular importance because early detection of AKI will allow for appropriate and timely interventions that would significantly decrease morbidity and mortality related to AKI.

**Advances and Limitations of Animal Models of Sepsis**

An ideal animal model of sepsis ought to consistently translate pertinent information from animal research to the human condition. As in many other fields of investigation, rodents have been a highly favored species in sepsis research. This is mainly because they are small, relatively inexpensive, and permit a large number of animals to be studied. Despite these advantages, certain rodent strains are quite resistant to endotoxin, have distinct hemodynamic profiles, and have smaller blood volume in comparison with humans, limiting the number of repeat samples that can be obtained from these species. The fact that there are differences between TLRs in mice and in humans could also affect interpretation of sepsis studies in the two species.

Parameters such as cardiac output and pulmonary artery pressure are measured more easily in larger species. There have been other animal species of induced sepsis that include rabbits, cats, dogs, pigs, sheep, and nonhuman primates (Tables 2 and 3). Unfortunately, none of the large or small animal species can completely reproduce the pathophysiology, immunology, and consequences of human sepsis. The majority of animal studies use young, healthy animals, and in most cases, the animals have no comorbidities and start with normal leukocyte counts. In addition, the clinical course of sepsis in humans is usually prolonged, taking days to weeks to manifest progressive organ failure. By contrast, the time course of illness in animal models ranges from hours to days, which may suggest a different set of pathophysiologic conditions. There is much to be improved in animal models of sepsis, and several key factors must be taken into consideration. These factors include the need for long-term studies with ICU-like conditions to simulate the often-delayed onset of organ dysfunction in the clinical setting and using sepsis or organ dysfunction criteria to start treatment instead of a fixed time schedule. Indeed, recent progress has been very encouraging and has led to several new clinically relevant animal models. Animal models will remain essential in the development of the testing and validation of all new therapies for sepsis and septic shock because they provide fundamental information about the pharmacokinetics, toxicity, and mechanism of drug action that cannot be duplicated by other methods.

**Table 1.** A partial list of emerging biomarkers for early detection of acute kidney injury

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Source of Sample</th>
<th>Elevation in Sepsis-induced AKI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystatin C</td>
<td>Plasma</td>
<td>Intermediate</td>
<td>44,76</td>
</tr>
<tr>
<td>L-FABP</td>
<td>Urine</td>
<td>Early</td>
<td>45,49</td>
</tr>
<tr>
<td>IL-18</td>
<td>Urine</td>
<td>Intermediate</td>
<td>35,36</td>
</tr>
<tr>
<td>NGAL</td>
<td>Plasma</td>
<td>Early</td>
<td>42,77</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Urine</td>
<td>Intermediate</td>
<td>44,48,76</td>
</tr>
<tr>
<td>Netrin-1</td>
<td>Urine</td>
<td>Early</td>
<td>46,47,78</td>
</tr>
</tbody>
</table>

L-FABP, L-type fatty acid–binding protein; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1.

**Table 2.** Most common animal models of sepsis

<table>
<thead>
<tr>
<th>Species</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodents</td>
<td>Small, inexpensive, defined genetic characteristics and transgenic strains</td>
<td>Difficult measurement of physiological parameters such as cardiac output, limited samples, major immunological differences</td>
</tr>
<tr>
<td>Sheep and pigs</td>
<td>Superior physiological, hemodynamic mimicry, easier to monitor important parameters, docile</td>
<td>More expensive, labor intensive</td>
</tr>
<tr>
<td>Nonhuman primates</td>
<td>Closely resemble human anatomy and replicate inflammatory response</td>
<td>Substantial expenses, ethical limitations, higher potential for zoonotic disease</td>
</tr>
</tbody>
</table>
RBF Alterations during Sepsis

Arterial vasodilation with an associated decrease in systemic vascular resistance is a fundamental hallmark of sepsis, and until recently, it was generally believed that like other causes of shock (hypovolemic or cardiogenic), sepsis-induced AKI was mainly due to hypoperfusion of kidneys. If true, this would imply restoration of such hypoperfusion, and RBF should be the primary means of renoprotection in sepsis.55

Most of our understanding regarding RBF during sepsis relies on animal models. Across these studies, the heterogeneous nature of animals used, methods of inducing sepsis, and observed changes in RBF that vary from unchanged, decreased, and markedly increased all translate to uncertainty regarding their applicability to humans.55,56 The characteristic pattern of RBF in human sepsis is for the most part largely unknown because RBF cannot be measured continuously in humans, and even its intermittent measurement requires a high level of invasiveness.55,57 However, a small cohort study where RBF was measured in patients with sepsis reported that RBF was either preserved or increased in these patients.58 This study and some others that followed seriously challenge the long-standing presumption that sepsis-induced AKI is mainly, if not completely, dictated by renal hypoperfusion.

In another study, investigators studied a percutaneously placed thermodilution RBF catheter in eight critically ill patients with AKI. Their major observation revealed that sepsis-induced AKI occurred despite normal RBF.59 These findings and the fact that septic patients typically show a high cardiac output and hyperdynamic circulation imply that observations in hyperdynamic models of sepsis are much more relevant to human septic shock.60 A major challenge to the conventional presumption that renal vasconstriction is an essential prerequisite for AKI during hyperdynamic sepsis came from a study where the authors studied the effects of sustained Gram-negative bacteremia and sepsis on RBF, renal vascular conductance, and renal function in male Merino sheep. They demonstrated that in addition to generalized peripheral vasodilation with increased cardiac output and decreased mean arterial pressure, there was renal vasodilation accompanied by a prominent increase in RBF. Despite this increase in RBF, however, creatinine clearance decreased significantly, and serum creatinine increased approximately fourfold.61

By monitoring the recovery phase and accompanying hemodynamic alterations, the same group of investigators took this concept one step further. In a well-controlled and comprehensive study, nine female sheep were instrumented to continuously record systemic hemodynamics and RBF.62 Most importantly, the hyperdynamic and normotensive circulation that was induced by bacterial (Escherichia Coli) challenge and fluid administration was accompanied by significant renal vasodilation and increased RBF. In spite of well-maintained renal perfusion, GFR deteriorated. In contrast, recovery from sepsis was characterized by normalization of GFR despite a renal vasoconstrictive response and return of the RBF back to control values. Such reduction of RBF and functional improvement in this model is an important finding, and the results indicate that the renal vascular bed participates in the systemic hemodynamic alterations not only during sepsis but also during its resolution. Previously, similar findings were observed in a pig model of sepsis that showed an increase in global RBF and an increase in medullary blood flow.63 These findings strongly suggest that the actual AKI that occurs during sepsis is a hyperemic injury.

A plausible explanation for these results could relate to the following considerations. Identical to the systemic arterioles that account for approximately two-thirds of total peripheral resistance, afferent and efferent arterioles are essential regulators of renal perfusion. Simultaneous dilation of both arterioles (with greater efferent than afferent dilation) can lead to decreased glomerular capillary pressure and subsequent decrease in filtration. This is very similar to the observed effects of angiotensin-converting enzyme inhibitors and may account for the AKI that accompanies sepsis.

Therapeutic Options for the Present and Future

Apart from supportive treatment (fluid management, antibiotics, vasopressors, diuretics, and dialysis), there have been a number of pharmacologic attempts directed at limiting and reversing sepsis-induced AKI. Anti-TNF therapy gained popularity particularly because of promising results in different animal models64–66 and the fact that elevated levels of soluble TNF receptors can independently predict the development of AKI and mortality.67 Nonetheless, several large clinical trials with neutralizing monoclonal anti-TNF antibodies and soluble TNF receptor fusion proteins failed to show survival benefits in pa-

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin injection</td>
<td>Sterile, simple, relatively stable, inexpensive, accurate dose can be measured</td>
<td>Restricted to Gram-negative bacteria, variable sensitivity among species, brief increase in inflammatory mediators</td>
</tr>
<tr>
<td>Intravascular infusion of live bacteria</td>
<td>Mimics extreme clinical sepsis, produces early hyperdynamic state, permits the study of the acute effects of early interventions</td>
<td>Strain specific effects, large doses are required, difficulty in analyzing pathophysiological pathways</td>
</tr>
<tr>
<td>Peritonitis models (CLP, fecal inoculation, and CASP)</td>
<td>Relatively simple and reproducible, mixed bacterial flora</td>
<td>Difficult to control the magnitude of sepsis, age, and strain variability</td>
</tr>
</tbody>
</table>

CLP, cecal ligation and puncture; CASP, colon ascendens stent peritonitis.
tients with sepsis. The same level of enthusiasm accompanied many other molecules that suggested their beneficial effects in preclinical models of sepsis. For example, inhibition of platelet-activating factor, endothelin, anti-thrombin, tissue factor pathway, leukocyte adhesion, and administration of natriuretic peptides and growth factors were all promising novel therapeutic approaches that unfortunately either never made it to clinical trials or failed to produce the desired effects in large clinical trials. Indeed, only one therapeutic agent, activated drotrecogin alfa, also known as recombinant human activated protein C, has been shown to improve survival in patients with severe sepsis and septic shock.

Mesenchymal stem cells (MSCs) are another novel approach that recently sparked great interest in the scientific community. MSCs or their microvesicles prove effective in various animal models of diseases including AKI. In addition to being immunosuppressive, their reparative effects are complex but are mainly mediated by paracrine mechanisms that act on surviving tubular cells by stimulating proliferation, migration, and ultimately differentiation into mature epithelial cells as well as by stimulating expansion and differentiation of resident progenitor stem cells. An ongoing clinical trial evaluating the safety and efficacy of MSCs in cardiac surgery-related AKI (clinicaltrials.gov, NCT00733876) reported the exciting initial results of their Phase I study at the American Society of Nephrology meeting in 2009. The successful delivery of MSCs to humans and the fact that they may be used allogeneically offer a novel therapeutic approach.

Recently, MSCs have been reported to have beneficial effects in sepsis-induced AKI in mice. These effects were attributed to prostaglandin E2-dependent reprogramming of host macrophages to increase their IL-10 production.

Another interesting approach has been the utilization of the stress-responsive heme oxygenase-1 (HO-1) enzyme system and the products of heme catabolism, including carbon monoxide, biliverdin, and bilirubin. These products have important antioxidant, anti-inflammatory, and antiapoptotic properties. For instance, HO-1-derived carbon monoxide enhances the host defense response to microbial sepsis in mice. A recent study demonstrated that high-mobility group box 1 contributes to lethality of endotoxemia in HO-1-deficient mice. A significant

Table 4. Partial list of emerging therapeutic targets tested in animal models

<table>
<thead>
<tr>
<th>Target</th>
<th>Primary mechanism</th>
<th>Agent</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMGB1</td>
<td>HMGB1 is released from damaged cells in sepsis, HMGB1 activates NF-kB via RAGE, TLR2, and TLR4</td>
<td>Neutralizing Ab</td>
<td>79</td>
</tr>
<tr>
<td>Lymphocyte apoptosis</td>
<td>Apoptosis induces depletion of immune cells, apoptosis impairs immunity by inducing anergy</td>
<td>Caspase inhibitor CD95 fusion-protein/siRNA</td>
<td>80</td>
</tr>
<tr>
<td>Pathogen recognition</td>
<td>E. coli sepsis induces cytokine production via TLR4; bacterial DNA induces cytokine production via TLR9</td>
<td>Neutralizing Ab ODN TLR9-inhibitor Chloroquine</td>
<td>81–83</td>
</tr>
<tr>
<td>End-organ damage</td>
<td>VEGF Systemic VEGF level increases in sepsis, VEGF-induced vascular leakage</td>
<td>Soluble Fit1</td>
<td>84–88</td>
</tr>
<tr>
<td>C5a</td>
<td>C5a induces lymphocyte apoptosis and coagulation system failure, C5a induces HMGB1 release via C5L2</td>
<td>Neutralizing Ab to C5a</td>
<td>89</td>
</tr>
<tr>
<td>Neuroimmune axis</td>
<td>Vagus nerve stimulation attenuates an inflammatory response via α7nAChR; acetylcholine inhibits HMGB1 release via α7nAChR</td>
<td></td>
<td>90,91</td>
</tr>
<tr>
<td>Pituitary hormones</td>
<td>α-MSH decreases inflammatory cytokines and NO production</td>
<td>α-MSH analog</td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Ghrelin decreases HMGB1 release and has antibacterial activity</td>
<td>Ghrelin</td>
<td></td>
</tr>
<tr>
<td>Cell-based therapy</td>
<td>NETs trap and kill bacteria in blood and tissue</td>
<td>Eritoran (TLR4 antagonist)</td>
<td>71,92</td>
</tr>
<tr>
<td>MSCs</td>
<td>TLR4 activation induces NET formation; MSC reprograms macrophage to produce IL-10</td>
<td>MSC</td>
<td></td>
</tr>
<tr>
<td>Heme oxygenase-system</td>
<td>Carbon monoxide acts as a potent anti-inflammatory molecule</td>
<td>Inhaled carbon monoxide</td>
<td>73–75</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Bilirubin is one of the most powerful antioxidants of the human body</td>
<td>Atazanavir (UGT1A1 inhibitor)</td>
<td></td>
</tr>
</tbody>
</table>

This table has been modified and reproduced with permission from Reference 48. HMGB 1, high mobility group box 1; RAGE, receptor of advanced glycation end product; ODN, oligonucleotides; nAChR, nicotinic acetylcholine receptor; α-MSH, α-melanocyte-stimulating hormone; NET, neutrophil extracellular trap; Fit1, Feline McDonough Sarcoma (FMS)-like tyrosine kinase 1 (also known as VEGF receptor 1); UGT1A1, 1 Uridine diphosphate glucuronosyl transferase enzyme; Ab, antibody; siRNA, small interfering; TLR, Toll-like receptor.
reduction of high-mobility group box 1 was noted after administration of carbon monoxide and biliverdin, products of the HO-1 enzymatic pathway. Moreover, HO-1 suppresses the infiltration of neutrophils in rat liver during sepsis.75 These and other findings have led to ongoing clinical trials that are examining the beneficial effects of carbon monoxide in AKI in the setting of delayed graft function in kidney transplantation (clinicaltrials.gov, NCT 00531856) and bilirubin in endotoxemia (clinicaltrials.gov, NCT 00916448). A few promising therapeutic approaches in sepsis-induced AKI are summarized in Table 4.

Concluding Remarks

Although sepsis is the most common cause of AKI in critical illness, there is limited information on sepsis-induced AKI. Over the past decades, intense research has introduced many anti-inflammatory drugs that proved effective in animal models but failed to translate to humans. Considering the very high and even growing number of patients with sepsis in the United States and other parts of the world, there is an urgent need for new approaches and treatment. Apart from activated protein C, there is no specific approved ancillary treatment for sepsis. There are certain key gaps in the field of sepsis-induced AKI that require further research and investigation (summarized in Table 5). Validation of novel biomarkers for early detection of sepsis-induced AKI and potentially restesting some of the therapeutic agents that were shown to be ineffective when creatinine-based detection of AKI was used may be timely and require reconsideration.

DISCLOSURES

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Table 5. Focus areas of interest in sepsis-induced acute kidney injury (AKI) research

| 1.          | Optimization of animal models that closely mimic human sepsis and AKI |
| 2.          | Role of immune modulation in sepsis-induced AKI |
| 3.          | Identification of specific biomarker profile for sepsis-induced AKI |
| 4.          | Appropriate fluid management in sepsis-induced AKI |
| 5.          | Retesting therapeutic interventions in sepsis-induced AKI using novel biomarkers rather than creatinine based changes |
| 6.          | Key endpoints in clinical trials of sepsis-induced AKI |


58. Bernard GR, Vincent JL, Laterre PF, LaRosa SP,


