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Emerging Therapeutic Targets of Sepsis-Associated Acute Kidney Injury

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Abstract

Sepsis-associated acute kidney injury (SA-AKI) is linked to high morbidity and mortality. Thus far singular approaches to target specific pathways known to contribute to the pathogenesis of SA-AKI have failed. Because of the complexity of the pathogenesis of SA-AKI, a reassessment necessitates integrative approaches to therapeutics of SA-AKI that include general supportive therapies such as the use of vasopressors, fluids, antimicrobial and target specific and time dependent therapeutics. There has been recent progress in our understanding of the pathogenesis and treatment of SA-AKI including temporal nature of pro- and anti-inflammatory processes. In this review, we will discuss the clinical and experimental basis of emerging therapeutic approaches that focus on targeting early proinflammatory and late anti-inflammatory processes as well as therapeutics that may enhance cellular survival and recovery. Lastly we include ongoing clinical trials in sepsis.

Keywords

Inflammation; cytokines; therapeutics; septic shock

Introduction

Sepsis is one of the most common causes of acute kidney injury (AKI) accounting for nearly 50% of cases of AKI in the intensive care unit (ICU)^{1,2} and is the leading cause of death in the ICU³. There are about 200,000 annual deaths attributable to sepsis in the US⁴. There is a bi-directional relationship between sepsis and AKI with an increased incidence of sepsis even in patients who develop AKI due to non-septic etiologies⁵. Standard treatment approaches such as parenteral antibiotic therapy, fluid resuscitation, and administration of vasopressor agents have not been effective in significantly reducing the incidence of SA-AKI or its associated mortality². Further, emergence of antibiotic-resistant microbes as well

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as the increased complexity of patients (additive comorbidities, advanced age and immunocompromised status) adds other dimensions to the problem and emphasizes the need to understand and devise novel therapeutic approaches to prevent and treat SA-AKI.

Traditional paradigm of sepsis-associated organ dysfunction and AKI has focused largely on specific cytokines and their modulation to improve outcomes in sepsis. Evidence from several studies published over the last two decades indicates that this singular approach is unlikely to be effective to improve outcomes. For example, clinical trials focused on antagonizing single inflammatory cytokines including: anti-endotoxin (LPS, lipopolysaccharide), anti-tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and Toll-Like receptor (TLR) 4 inhibitors have been unsuccessful⁶⁻⁸.

Based on pre-clinical and human studies, there has been significant recent progress in our understanding of novel pathways that are involved in the pathogenesis of SA-AKI. In this review, we will discuss preclinical studies that have a strong pathophysiological basis as well as recent ongoing clinical trials in sepsis and AKI. In particular, understanding time-dependent processes and multiple targets suggests that successful outcomes may depend on an integrated approach to the treatment of sepsis (Table 1). Lastly, therapeutic targets such as TNF, IL-1 β , TLRs etc have been described in recent reviews^{4,9} and will not be discussed here.

Overview of Inflammation

The inflammatory response to sepsis and trauma remains controversial¹⁰. Lewis Thomas was responsible for a paradigm shift by changing the focus from pathogens to the pathological dysregulated host response that serves as the basis for the clinical expression of the systemic inflammatory response syndrome¹¹ and sepsis. The host responds to danger associated molecular patterns (DAMPs) or pathogen associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), flagellin, double-stranded RNA, and CpG DNA¹² which are ligands for pattern recognition receptors, such as Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs)^{13,14} that activate innate immunity. Early deaths are due typically to a hyper-inflammatory 'cytokine storm' response with clinical features such as fever, circulatory collapse, acidosis and hypercatabolism. The initial degree of inflammatory response depends on a number of factors that include pathogen virulence and bacterial load and the patient's baseline comorbid conditions and genetic background¹⁵.

Late deaths may be due to pronounced immunosuppression and T cell exhaustion^{10,16}. Patients who died of sepsis in the ICU when compared to control patients who were declared brain dead or had emergent splenectomy due to trauma, had splenocytes that had significant reductions in secretion of TNF, interferon gamma (INF- γ), IL-6, IL-10¹⁶. There was also reduced CD28 expression, a costimulatory molecule that activates T cells, increased PD-1 expression, a molecule that negatively regulates T cell activation and T cell proliferation, increased CTLA-4 expression, a receptor that down regulates the immune response and lastly reduced IL-7Ra¹⁶. Thus, therapeutic approaches should consider temporal changes in

immune responsiveness; suppression of early inflammation and enhancing late immunity (Figure 1).

Targeting Early Inflammation

Alkaline phosphatase

Recent studies by Pickers et al. have suggested a novel approach targeting inflammation in SA-AKI^{17,18}. In their preclinical and clinical studies, these authors have used systemic alkaline phosphatase administration as an anti-inflammatory strategy to demonstrate protection in SA-AKI. Alkaline phosphatase is thought to neutralize bacterial endotoxin through direct dephosphorylation of endotoxin. Furthermore, alkaline phosphatase catalyzes the conversion of the danger molecule, adenosine triphosphate (ATP), into adenosine, a potent anti-inflammatory factor. Activation of adenosine 2a receptors have potent antiinflammatory effects^{19,20} and synthetic analogs block AKI^{21,22} and improve survival in sepsis²³. In a recent phase IIa studies, administration of recombinant alkaline phosphatase resulted in reduced inflammation and decreased SA-AKI although there were no changes in mortality^{17,18}. If these provocative findings can be confirmed in large-scale clinical trials, it will provide a new strategy to prevent and treat SA-AKI.

Endocannabinoid Receptors (cannabinoid 2 (CB2))

The endocannabinoid system represents a unique target for the treatment of sepsis. This system is an endogenous signaling system that modulates a variety of functions including the immune system. The two most important receptors are G-protein coupled receptors, cannabinoid 1 (CB1) and cannabinoid 2 (CB2), are linked to Gi, which inhibit adenylyl cyclase and intracellular cAMP accumulation²⁴. Whereas CB1 receptors are expressed primarily in the central nervous system²⁴, CB2 receptors are expressed on leukocytes and regulate the immune system^{25–27}. CB2 receptor activation attenuates leukocyte endothelial cell interaction and recruitment of leukocytes and reduces proinflammatory mediators^{28–31}. Using cecal ligation puncture (CLP) model of sepsis, CB2 receptor deficient mice had increased mortality, lung injury, and neutrophil recruitment at the site of infection³². A highly selective CB2 receptor agonist, *N*-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-1,4-dihydro-6-methylindeno[1,2-*c*]pyrazole-3-carboxamide (GP1a) (*K_i* values for this compound are 0.037 and 363 nM for the CB2R and CB1R, respectively) reduced inflammation, bacterial colony count and improved survival time³². In humans, administration of lipopolysaccharide leads to an increase in endogenous cannabinoid, anandamide³³ suggesting a potential role for CB2 receptor agonists for the treatment of sepsis.

PPAR alpha agonists

Peroxisome proliferator-activated receptor-alpha (PPAR α), a member of the nuclear receptor superfamily of ligand-dependent transcription factors related to retinoid, steroid, and thyroid hormone receptors³⁴. Fibrates are ligands for PPAR α receptors and have been shown to have anti-inflammatory properties. They have known effects on classically activated macrophages to block AP1 and NKF-K β signaling^{35,36} and inhibit proinflammatory molecules including IFN- γ and IL-17^{37,38}. In animal models of AKI,

fibrates protect from cisplatin induced AKI³⁹ by preventing proximal tubule cell death⁴⁰. In SA-AKI, fibrates have been shown to ameliorate bacterial sepsis induced by *Salmonella typhimurium* by promoting neutrophil recruitment via CXCR 2⁴¹. LPS induced down regulation of CXCR2 was blocked increasing neutrophil influx, decrease bacterial count and improved survival. Thus enhancing bacterial clearance while potentially preserving proximal tubule survival might be good combination for SA-AKI.

Neuro-Immune Activation-the Cholinergic Antiinflammatory Pathway

The nervous system controls inflammatory responses through a reflex circuit in which afferent signals sense inflammation and efferent signals quell inflammation^{42,43} (Figure 2). This anti-inflammatory pathway referred to as the cholinergic antiinflammatory pathway (CAP) has recently been described⁴⁴. Afferent and efferent signals are transmitted by the vagus nerve in response to DAMPS or PAMPS. Activation of the splenic nerve stimulates the production of acetylcholine by a splenic CD4⁺ subset within the white pulp via β -adrenergic receptors activation. Acetylcholine then traverses into the red pulp and activates α -7 nicotinic acetylcholine receptors (α 7nAChRs) expressed on splenic myeloid/macrophages. Binding of acetylcholine to α 7nAChRs on nearby myeloid/macrophages cells results in suppressed splenic, and in turn, systemic cytokine (proinflammatory cytokines such as TNF α , IL1 β , High Mobility Group Box 1 (HMGB1) levels during inflammation (both sepsis and other inflammatory diseases). Experimental studies demonstrate that stimulation of the vagus nerve attenuates cytokine release in sepsis, IRI and other states of inflammation and nicotine, an α 7nAChRs agonist, reduces mortality in sepsis^{45,46}. The current methods used to directly stimulate the cholinergic anti-inflammatory pathway are limited to administration of nonspecific cholinergic agonists or surgical methods to stimulate the vagus nerve⁴⁷. Recently, a modified ultrasound regimen activated the CAP and protected kidneys from IRI⁴⁸ (Figure 2). In this study, anesthetized mice were exposed to an ultrasound (US) protocol 24 hrs prior to renal ischemia. After 24 hrs of reperfusion, US-treated mice had marked attenuation of plasma creatinine, inflammation and preserved morphology compared to sham US-treated mice. This marked protective effect was observed even when mice were exposed to the same US regimen 48 hours prior to ischemia. There was marked reduction in interstitial fibrosis, which suggests that this treatment may retard progression of AKI to CKD/ESRD. Renal protection against IRI depended on splenic CD4⁺ T cells and α 7nAChR-expressing cells. Splenectomy abrogated the protective effect of US against AKI. These results strongly support the concept that CAP is important in attenuating AKI and that a simple modified nonpharmacologic, noninvasive, ultrasound-based method may reduce AKI. Preliminary results suggest that this US regimen may protect from sepsis-associated AKI (unpublished observations, Gigliotti and Okusa, 2014).

Soluble Thrombomodulin

Healthy endothelial cells maintain regional microcirculation and prevent thrombosis through thrombomodulin-protein C system⁴⁹. Endothelial dysfunction from AKI or sepsis, leads to microvascular flow changes and tissue hypoperfusion, tissue hypoxia and inflammation⁵⁰. Thrombomodulin (TM) is a 557 amino acid glycoprotein expressed broadly on surface of endothelial cells exert thromboresistance resulting in anticoagulation⁴⁹. On the cell surface, thrombin-mediated cleavage of protein C requires TM as a co-factor generating activated

protein C (APC). APC is an important modulator of coagulation and inflammation associated with sepsis by inactivating factor Va and VIIIa, thereby promoting fibrinolysis and inhibiting thrombosis. In clinical studies of sepsis the use of APC was associated with a significant increase in bleeding risk⁵¹. Soluble TM may exert local effects to activate protein C and prevent regional coagulation events without systemic effects. Recent studies have demonstrated that sTM was effective in preventing and treating establish AKI, an effect associated with reduced leukostasis and endothelial cell permeability⁵². The mechanism of protection was independent of the generation of APC, as a sTM variant, unable to activate rat PC, was effective as wild-type sTM in preserving renal function. Although the data suggest that the protective effect is independent of its anticoagulant effect, sTM may exert its effect by several means. sTM may have anti-inflammatory effects; studies using N-terminal lectin-like domain of TM, which lacks anticoagulant function, block leukocyte adhesion to endothelial cells⁵³. In addition sTM may have cytoprotective and antiinflammatory effects through activating endothelial cell protein C receptor/protease activated receptor (EPCR/PAR) signaling. Lastly sTM inactivates C3a or C5a and blocks inflammation⁴⁹. Thus additional studies are necessary to delineate the mechanism of action of sTM while clinical studies are ongoing to demonstrate its efficacy in sepsis (Table 2).

Cell-Based Therapies

Severe sepsis is characterized by multiorgan dysfunction in critically ill patients leading to septic shock a condition that is complicated by hypotension unresponsive to fluid resuscitation and vasopressors. In these instances there is marked dysregulation of the immune response as a result of cytokine, chemokine, complement activation products and intracellular alarmins^{10,54–56}. The myriad number of cytokines that contribute to the dysregulated state of sepsis necessitates combining multiple targets in treating sepsis^{55,57}. Cell-based therapy may lead to the broad ability to block the innate immune response by targeting multiple sites. Stem cells are unspecialized or undifferentiated precursor cells that have the capacity for self-renewal and can differentiate into different cell types⁵⁸. Mesenchymal stem cells (MSCs) are the best studied. These cells are generated in bone marrow and can differentiate into osteocytes, chondrocytes and adipocytes and their use in therapeutics takes advantage of their pluripotency, hypo-immunogenicity, easy accessibility from bone marrow and rapid ex vivo expansion. When MSCs were infused they have been shown to protect and enhance recovery in cisplatin, glycerol and IRI^{59–63}. In solid organ transplantation, preclinical studies demonstrate a potent effect of MSCs factors that contribute to transplant tolerance. Based upon these findings preclinical studies are underway and may be effective in reducing the risk of acute rejection^{64,65}.

Although they have the capacity for transdifferentiation, the observation thus far is that the number of differentiated stem cells that contribute to tissue protection/repair are low and the tissue protective effects are most likely due to paracrine mechanisms including growth factors, cytokines that modulate mitogenesis, apoptosis, inflammation and vasculogenesis and angiogenesis^{62,66–69}. MSCs have been shown to enhance proliferation of endogenous tubule epithelial cells through soluble factors⁶³. Recently microvesicles derived from MSCs have been shown to shuttle mRNA to injured cells to enhance survival⁷⁰. In experimental sepsis, MSCs reduce inflammation and AKI^{71,72}.

Other forms of cell-based therapies may be useful in sepsis, primarily to quell the early proinflammatory state. Regulatory CD4⁺CD25⁺ T cells (Tregs) suppress inflammatory conditions including AKI⁷³ through cell to cell contact and cytokine independent mechanisms (see review by⁷⁴. When T regulatory cells are stimulated in vivo in a cecal ligation puncture model of sepsis and administered to mice in prevention or therapeutic mode they have been shown to improve survival and bacterial clearance⁷⁵.

Dendritic cells (DCs) are a heterogeneous bone-marrow derived antigen presenting cells. They have distinct maturation and activation states and have the potential to induce immunity or tolerance^{76,77}. Tolerogenic DCs have the capacity to present antigen to antigen specific T cells but are unable to adequately provide costimulatory signals that lead to T cell activation and proliferation. Tolerogenic DCs are potentially useful in graft versus host disease, autoimmune disease, and transplant tolerance⁷⁸. Recently DCs were tolerized by adenosine 2a agonist treatment that attenuated kidney IRI²². Generating tolerized DCs can be achieved through treatment with growth factors and cytokines (TGFβ, IL-10, VEGF), genetic engineering (sphingosine 1-phosphate 3 deficiency, NF-κB oligonucleotides), pharmacological agents (calcineurin inhibitors, adenosine 2a agonists)^{22,78,79}. Its use in attenuating the dysregulated cytokine response during sepsis has not yet been tested.

Targeting Late Immune Suppression

The importance of temporal nature of sepsis has important implications regarding therapeutic intervention. The concept that hyperimmune response characterizes early sepsis necessitates early anti-inflammatory approaches. However, late in the course of sepsis the marked immunosuppressive state requires interventions that stimulate the immune response such as IL-7, PD-1/PD-1 antibodies and other immunoadjuvants.

Interleukin - 7

IL-7 is critical for T cell development and function and its effects are mediated by heterodimeric IL-7Rs which are expressed on human T cells, central memory T cells and T regulatory cells⁸⁰. In sepsis models, IL-7 enhances immunity by: increasing expression of cell adhesion molecules facilitating leukocyte trafficking to sites of infection, increasing T cell activation and proliferation, preventing T cell apoptosis and T cell depletion and restoring T cell IFN-γ production^{81,82}. In humans, ex vivo treatment of human lymphocytes increases cell proliferation, IFN-γ production, Bcl-2 induction and T cell diversity, factors that enhance immune response to pathogens^{83–85}.

PD-1/PD-1L antibodies

In sepsis, there is an increase in inhibitory program cell death 1 (PD-1 and its ligand (PD-L1) that could contribute to immune suppression in late sepsis through T cell exhaustion^{3,86}. When blood from septic and non septic patients were assessed by flow cytometry, septic patients had a higher percentage of CD4⁺, CD8⁺PD-1 expression and monocyte-PDL-1 expression. This was associated with a decrease in lymphocyte IFN-γ and IL-2 expression. Anti-PD1 and anti-PD1L antibody increased IFN-γ, IL-2 production and decreased lymphocyte apoptosis⁸⁶. In animal models of sepsis, PD-L1 deficient mice⁸⁷) or using anti-

PD-1⁸⁸ or anti-PD-L1 blocking antibody improves survival. In cancer, T cell exhaustion appears to contribute to the immunosuppressed state, thus given the efficacy and safety profile of anti-PD-1 and anti-PD1L in cancer clinical trials^{89,90} and preclinical efficacy in sepsis, these results suggest the potential use in anti-PD1 and anti-PD1L antibody in clinical trials to augment immune responsiveness in sepsis.

Other immunoadjuvants

Interleukin 15, an immunoadjuvant molecule similar to IL-7, has important effects on natural killer cell (NK) cell development, survival and function, as well as NK cell cytotoxicity⁹¹. In sepsis, IL-15 decreases apoptosis of immune cells similar to IL-7⁹². Granulocyte macrophage colony-stimulating factor (GM-CSF) has been shown to enhance immune function in septic patients. Neutrophils are the primary host defense against infection and during sepsis neutrophil function appears to be defective^{93–95}. In clinical studies of sepsis, GM-CSF restores monocyte function^{96,97} and shortens time of mechanical ventilation and hospital ICU stay⁹⁶. Thus these studies support the need for additional human studies in septic patients.

Cell survival: Oxidative stress, mitochondria and anti-oxidant strategies

Iron

Iron contributes to host intracellular and extracellular and as well as microbial function during sepsis (Figure 3). While catalytic (also referred to as labile) iron is injurious to cells through its ability to undergo redox cycle and induce oxidative radicals⁹⁸, various physiologic intracellular processes such as mitochondrial function, cell cycle and deoxyribonucleic acid (DNA) repair are iron-dependent⁹⁹. Similarly, microbes secrete molecules called siderophores to capture iron for their growth and survival. Iron starvation of the microbe is a sentinel strategy adopted by the body to counter infection and sepsis¹⁰⁰. Cells synthesize iron-sequestering proteins such as neutrophil gelatinase-associated protein (NGAL) to outcompete microbial response. Iron sequestration is also achieved through the release of hepcidin, an antimicrobial peptide released from the liver. Hepcidin downregulates iron export protein, ferroportin, to induce reticuloendothelial iron sequestration¹⁰¹. Macrophages act as a safe reservoir to store iron in its non-toxic in ferritin. In murine infection models such as in malarial infection, hepcidin overexpression is effective in limiting the progression of infection^{102,103}. Further, hepcidin treatment and subsequent macrophage iron sequestration has been shown to inhibit lipopolysaccharide (LPS)- and sepsis-induced pro-inflammatory response¹⁰⁴. However, it is unknown if hepcidin treatment would induce protection against sepsis-induced kidney injury. Also, there is only limited data on using iron chelation to treat sepsis or its complications¹⁰⁵. Iron chelation with desferrioxamine induced protection against sepsis-associated mortality and this was associated with paradoxical upregulation of the pro-apoptotic factor, Bax¹⁰⁶.

Hypoxia-inducible factor (HIF)

Progression of sepsis results in cellular oxygen deprivation constitutes the end-result of sepsis. In response to hypoxia, HIF is induced. Further, HIF is upregulated through pathways involving the key immune response regulator nuclear factor-kappaB (NF-κB)¹⁰⁷.

Of the various isoforms, HIF-1 α activation induces the release of pro-angiogenic VEGF and vasoconstrictors like endothelin-1. Further, LPS induces HIF-1 α by inhibiting prolyl hydroxylase (PHD) expression. HIF-1 α promotes production of pro-inflammatory cytokines and is a key mediator of the host response to sepsis¹⁰⁸. It was recently demonstrated that PHD3 rather than PHD1 inhibition more specifically worsened sepsis-associated innate immune responses and outcome, in a HIF-1 α - and NF- κ B-dependent manner. Anti-cancer drug, 2-methoxyestradiol, known to inhibit HIF-1 α - and NF- κ B, was recently shown to be protective in a murine sepsis model. 2-methoxyestradiol therapy prevented sepsis-associated mortality and complications including AKI¹⁰⁹.

HIF-2 α activation results in the release of erythropoietin, which in addition to its known ability to induce erythropoiesis is also a cytoprotective molecule. Very little is known on the effect of modulating HIF-2 α in sepsis.

Heme oxygenase

Heme proteins, universally present in cellular compartments of different organ systems, perform vital functions such as oxygen transport and mitochondrial electron transport. With cell injury, as heme proteins are released from the cells, heme dissociates with ease from the globin moiety. Free heme is cytotoxic and inducible heme oxygenase-1 (HO-1) and constitutive heme oxygenase-2 (HO-2) degrades free heme into cytoprotective molecules including bilirubin and carbon monoxide (CO). This reaction, further, results in the generation of free iron, and induction of cytoprotective ferritin¹¹⁰. Genetic deficiency of HO-1 results in more severe AKI after rhabdomyolysis, ischemia or endotoxemia. Chemical (heme arginate) or genetic induction of HO-1 protects against kidney injury. Reduction in renal injury mediated through HO-1 is thought to involve three complementary mechanisms: 1) reduction in the endogenous heme; 2) generation of cytoprotectants (bilirubin, CO and ferritin) and 3) modulation of iron homeostasis^{111,112}. Macrophage HO-1 is likely to play a critical protective function in AKI as heme arginate, known to induce HO-1 in macrophages *in vitro* and *in vivo*, mitigated age-dependent sensitivity to AKI. Similarly, macrophages with adenoviral overexpression of HO-1 also protected against ischemic kidney injury and HO-1 overexpression improved the anti-inflammatory and phagocytic function of macrophages¹¹³. HO-1 might also be protective in AKI through its suppressive effects on tubuloglomerular feedback. Recently, mitochondria-specific expression of HO-1 was shown to be protective in ischemic AKI¹¹⁴. In murine endotoxemia model, inhibition of HO-1 with zinc protoporphyrin resulted in a paradoxical protective response with improved systemic hemodynamics, increased renal blood flow and better glomerular filtration rate¹¹⁵. This apparent paradox is attributed to the prevention of CO-mediated vasodilatation by HO-1 inhibition. In another study, it was shown that while HO-1 deficiency was associated with better systemic hemodynamics, it resulted in worse LPS-induced mortality¹¹⁶.

Mitochondrial ROS

Recent studies by Holthoff et al., indicate that SA-AKI is associated with reduction in renal blood flow (RBF), which is characterized by compromised circulation in the capillaries adjacent to the tubules that demonstrate increased inducible nitric oxide synthase (iNOS) and nitrosative oxidative stress¹¹⁷. Furthermore, in a cecal ligation picture model of sepsis,

selective inhibition of iNOS prevented tubular oxidative stress and reversal of microcirculatory abnormalities. Although further work needs to be done to understand the link between tubular epithelial oxidative stress and microcirculatory dysfunction, therapeutic importance is supported by the observation that use of resveratrol, a scavenger of peroxynitrite and superoxide, is protective against SA-AKI. Resveratrol treatment diminished tubular oxidative stress, improved microcirculatory flow, prevented sepsis-associated kidney pathology and improved survival¹¹⁷. There are other redox-based compounds such as lactoferrin, selenium, pentoxifylline and edaravone that have shown benefit in pre-clinical models¹¹⁸.

Mitochondrial biogenesis

Tran et al have confirmed sepsis-associated reduction in RBF in their recent study¹¹⁹. However, in their study, tissue oxygenation remained intact despite reduced RBF as kidney oxygen consumption was diminished. The authors demonstrated impaired mitochondrial function with reduced expression of PPAR- γ coactivator-1 α (PGC-1 α), a regulator of mitochondrial biogenesis, in SA-AKI. There was a marked functional to structural dissociation as tubular cells with severe mitochondrial dysfunction demonstrated little demonstrable pathology. Tumor necrosis factor- α (TNF- α) reduced PGC-1 α and oxygen consumption and overexpression of PGC-1 α corrected the mitochondrial defect. Of note, resveratrol is also known to induce mitochondrial biogenesis¹²⁰.

Collectively, these studies stress the central importance of targeting iron and heme homeostasis and optimizing kidney mitochondrial function in preventing and treating SA-AKI.

Molecular mechanisms of recovery

While multiple cellular pathways get activated during organ repair and recovery after sepsis, mitochondrial biogenesis, autophagy induction and resumption of cell cycle play vital roles. Here, we will review the role of cell cycle and autophagy in sepsis recovery.

Cell cycle

Induction of cell cycle arrest in G1 phase is a key mechanism for cell death and AKI in sepsis. In fact, urine levels of insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), both inducers of G1 cell cycle arrest, were identified as powerful biomarkers of SA-AKI¹²¹. In murine models of sepsis, G1 cell cycle arrest was shown to play a role in the initiation of sepsis-associated AKI and cell cycle progression through phosphorylation of retinoblastoma gene was shown to be involved in the recovery of AKI¹²².

Autophagy

Successful cellular recovery requires cleaning up internal and external cellular debris. Autophagy is a process whereby damaged internal organelles such as mitochondria are processed by lysosomal autophagy apparatus to facilitate cell survival. While uncontrolled autophagy itself might contribute to organ dysfunction, a successful and limited autophagy

response triggers an antiinflammatory response and tissue repair. Inhibition of autophagy in sepsis leads to accumulation mitochondrial DNA and NALP3 inflammasome activation¹²³. Mice deficient in autophagy (LC3B deficient mice) were more susceptible to LPS-induced mortality¹²³. LC3 overexpression was shown to improve survival and reduce lung injury through increased autophagosome clearance¹²⁴. In murine models of sepsis, induction of autophagy with either temsirolimus, a target of rapamycin (mTOR) inhibitor or AICAR, an adenosine monophosphate kinase (AMPK) inhibitor, protected against the development of sepsis-associated AKI¹²⁵. More recently, low doses of anthracycline, a cancer chemotherapy drug, were shown offer robust protection against sepsis by triggering DNA damage-mediated protective response and autophagy¹⁰².

Ongoing clinical trials in sepsis

Similar to the experience with finding effective therapeutics for acute kidney injury (AKI), the treatment of sepsis has been limited to therapy of the underlying inciting factors with no pharmaceuticals or other strategies found to be effective in all patients. In fact, initially promising therapies such as drotrecogin alfa (a recombinant form of human activated protein C) have now been withdrawn from the market after failing to demonstrate a survival benefit in a follow-up clinical trial subsequent to the initial registration study¹²⁶ (<http://www.fda.gov/Drugs/DrugSafety/ucm277114.htm>). This does not mean that the search for effective therapeutics has ceased and a search of www.clinicaltrials.gov in May 2014, listed 1328 studies in sepsis of which 560 were open and 343 involved an active intervention to improve outcomes.

Many of these therapeutic strategies attempt to modulate the body's innate immune response during sepsis (Table 2 is a partial list of these trials). An example of a promising but failed attempt at developing therapeutics in this area was drugs targeting toll-like receptors (TLRs). These are pattern-recognition receptors on the surface of immune cells that recognize highly conserved molecules, such as lipopolysaccharide (LPS) or peptidoglycans on the surface of microbes. This recognition leads to widespread activation of the immune response, which may be excessive and contribute to poor outcomes¹²⁷. Thus, targeting TLRs would seem an attractive strategy to mitigate the excessive inflammatory response associated with sepsis. Unfortunately, a recent notable failure with this approach was with the drug eritoran (synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor), which had demonstrated promising preclinical data¹²⁸. In a large, multicenter randomized trial (ACCESS trial), eritoran failed to show any benefit in 28-day mortality over placebo⁶. Other strategies that aim to modify the immune response and are in various stages of development include: drugs targeting bacterial superantigens (AB103)^{129,130}, immunomodulatory proteins (talactoferrin)¹³¹ http://agennix.com/index.php?option=com_content&view=article&id=205%3Aagennix-ag-halts-phase-iiiii-oasis-trial-in-severe-sepsis&catid=23%3Apress-releases-2012&Itemid=56&lang=en (accessed May 18, 2014), and anticoagulant pathways (ART-123)¹³², as well as blocking complement activation (C1-esterase inhibitor)¹³³, and inhibiting inflammatory cytokines (CytoFab against tumor necrosis alpha)¹³⁴. Trials for these agents are in various stages (Table 2).

Another novel approach has been based upon the finding that late sepsis-related deaths appear to be often associated with evidence of immune suppression and dysfunction^{10,135}. Thus, those patients that survive the initial pro-inflammatory stage may enter an anti-inflammatory phase with variable degrees of “immunoparalysis.” To counter this phase, immune enhancement or immunoadjuvant strategies are being studied. Agents that are being studied include: interferon (IFN)-gamma¹³⁶, granulocyte colony-stimulating factor (GM-CSF)³, interleukin (IL)-7⁸³, IL-15⁹², anti-PD (programmed cell death receptor)-1⁸⁸ and anti-BTLA (B and T lymphocyte attenuator)¹³⁷. An important aspect of these immunoadjuvant therapies may be that biomarkers to identify the immune suppressed stage of sepsis will have to be incorporated into treatment algorithms¹³⁵. This ensures that these agents will not further enhance the pro-inflammatory stages of sepsis and are targeted to specific defects in immune function.

There are a host of other compounds that are being actively studied for the treatment of sepsis with details in Table 2. These include: heparin^{138,139}, statins^{140,141}, pentoxifylline¹⁴², beta-blockade¹⁴³, dexmedetomidine¹⁴⁴, acetaminophen¹⁴⁵, selenium^{146,147}, L-citrulline¹⁴⁸, L-carnitine¹⁴⁹, zinc¹¹⁸, hydrocortisone^{150,151}, melatonin¹⁵², vitamin D¹⁵³, thiamine¹⁵⁴, and vitamin C¹⁵⁵. Several of these trials test the concept as to whether pharmaconutrients given in large doses can improve outcomes in sepsis through anti-oxidant and anti-inflammatory mechanisms¹⁴⁷.

Of note, many of the ongoing studies are small or pilot trials that are likely underpowered to determine clinical efficacy while some trials aim to explore outcomes with drugs that have had contradictory results in prior trials (such as with corticosteroids and heparin). Given the increased understanding of the mechanisms involved in sepsis it is likely that there will be continued growth in clinical trials to determine efficacy of these targeted approaches.

Conclusions

The successful treatment of SA-AKI necessitates an integrative therapeutic approach that takes into consideration the temporal nature of systemic immune response and local kidney specific factors. Single therapies are unlikely to be effective and nearly all have failed in the past. Thus timely intervention of general measures such as antibiotics, fluids, and vasopressors are required. In addition attenuating the profound proinflammatory response as well as the activating late immune suppressive response may complement these general measures. Lastly interventions to enhance cell survival and enhance cellular recovery provide the best opportunity for improving outcomes in SA-AKI.

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Figure 1. Immune responsiveness following sepsis

The host response to sepsis and septic shock is an early dysregulated immune response that is mediated via activation of innate immunity followed by a state of immunosuppression. Therapeutics should consider the temporal profile of the immune status. Early blockade of proinflammatory pathways should be followed by late activation of immunity.

Figure 2. Cholinergic Anti-inflammatory Reflex

The cholinergic antiinflammatory reflex regulating immunity is initiated by DAMPs and PAMPS that activate the afferent signaling pathway of the vagus nerve to the nucleus tractus solitarius. Neural signals are sent to the hypothalamus and brainstem and efferent signals emanate from the ambiguous and dorsal motor nucleus and travel down the vagus nerve (for a review see¹⁵⁶). Activation of the adrenergic splenic nerve results in the release of norepinephrine, which binds to adrenergic receptors on nearby CD4⁺ T-cells. This stimulates the production of acetylcholine that binds to $\alpha 7$ nAChRs on splenic myeloid cells (macrophages) and results in suppression of the synthesis and release of proinflammatory mediators such as TNF, IL-1, IL-18, HMGB1, chemokines and other cytokines. Nicotine, an $\alpha 7$ nAChR agonist, mimics the effect of Ach. A simple US regimen is thought to activate the splenic cholinergic reflex and attenuate kidney IRI⁴⁸. US – ultrasound, NE - norepinephrine, ACh – acetylcholine.

Figure 3. Iron homeostasis and sepsis

Microbes secrete siderophores to capture iron required for their growth and survival. Hosts secrete NGAL to mediate antimicrobial response through iron starvation. Sepsis-associated inflammatory response induces release of antimicrobial peptide, hepcidin, from the liver. Heparidin downregulates ferroportin to induce reticuloendothelial iron sequestration, which in turn leads to decreased availability of extracellular iron for microbial growth. Iron sequestration in macrophages also results in attenuated pro-inflammatory response to endotoxemia and sepsis. Dysregulated iron homeostasis would result in oxidative stress and worse sepsis-associated end organ injury. Iron chelation might be of therapeutic benefit in decreasing oxidative stress induced damage. NGAL, Neutrophil gelatinase-associated lipocalin.

Table 1**Therapeutic Targets in Septic AKI****Attenuating Early Inflammatory Response**

- 1 Endocannabinoids
- 2 PPAR alpha agonists
- 3 Neuroimmune activation
- 4 Soluble Thrombomodulin
- 5 Cell-based therapy
 - a. Mesenchymal stem cells
 - b. Regulatory T cells
 - c. Tolerized dendritic cells

Activating Late Immunity

- 1 Interleukin - 7
- 2 Interleukin - 15
- 3 GM-CSF

Cellular Targets

- 1 Iron
- 2 Hypoxia inducible factor (HIF1 α and HIF 2 α)
- 3 Heme oxygenase
- 4 Mitochondria Reactive Oxygen Species
- 5 Mitochondrial Biogenesis

Molecular mechanisms of recovery

- 1 Autophagy
- 2 Cell cycle

Table 2

Selected trials of therapeutics for sepsis

Trial Name	Identifier and Status	Description
Phase 3 Safety and Efficacy Study of ART-123 in Subjects With Severe Sepsis and Coagulopathy	NCT01598831 Recruiting	Recombinant thrombomodulin (ART-123) was found to be a safe intervention in critically ill patients with sepsis and suspected disseminated intravascular coagulation. A phase 2b study provided evidence suggestive of efficacy supporting further development of this drug in sepsis-associated coagulopathy including disseminated intravascular coagulation ¹³²
Safety and Efficacy of Talactoferrin Alfa in Patients With Severe Sepsis (OASIS)	NCT01273779 Suspended	Talactoferrin alfa, a recombinant form of human lactoferrin, has anti-infective and anti-inflammatory properties and plays an important role in maintaining gastrointestinal mucosal barrier integrity. In experimental animal models, administration of talactoferrin reduces translocation of bacteria from the gut into the systemic circulation and mortality from sepsis ¹³¹ . However, the phase II/III trial was halted due to higher 28-day mortality rate in the talactoferrin group.
A Study to Compare the Efficacy and Safety of 2 Dosing Regimens of IV Infusions of AZD9773 (CytoFab™) With Placebo in Adult Patients With Severe Sepsis and/or Septic Shock	NCT01145560 Completed	The polyclonal ovine anti-TNF Fab fragments (CytoFab) has the ability to neutralize tumor necrosis factor and decrease the TNF-dependent production of interleukin-6 (IL-6) and interleukin-8 (IL-8) ¹³⁴ . In a preliminary study CytoFab reduced TNF- α and IL-6 levels and increased the number of ventilator-free and intensive care unit (ICU)-free days at day 28 ¹³⁴
Evaluation of Safety, PK and Immunomodulatory Effects of AB103 in Necrotizing Soft Tissue Infections Patients	NCT01417780 Active, not yet recruiting (May 2014)	AB103 is a novel synthetic CD28 mimetic octapeptide that selectively inhibits the direct binding of superantigen exotoxins to the CD28 costimulatory receptor on T-helper lymphocytes. Preclinical studies demonstrated that AB103 and related superantigen mimetic peptides are associated with improved survival in animal models of toxic shock and sepsis. A preliminary trial in patients with necrotizing soft-tissue infections showed improvements in illness severity score and overall safety of the agent ¹³⁰
Effects of Alkaline Phosphatase on Renal Function in Septic Patients	NCT00457613 Completed	Alkaline phosphatase is able to reduce inflammation through dephosphorylation and thereby detoxification of endotoxin (lipopolysaccharide), which is an important mediator of sepsis. Second, adenosine triphosphate, released during cellular stress caused by inflammation and hypoxia, has detrimental effects but can be converted by alkaline phosphatase into adenosine with anti-inflammatory and tissue-protective effects. Phase 2a clinical trials have demonstrated benefit in reducing sepsis-associated AKI ¹⁷ .
In Vivo Effects of C1-esterase inhibitor on the Innate Immune Response During Human Endotoxemia - VECTOR II	NCT01766414 Not yet opened (May 2014)	C1-esterase inhibitor, an endogenous acute-phase protein, regulates various inflammatory and anti-inflammatory pathways, including the kallikrein-kinin system and leukocyte activity. A preliminary study assessed the influence of high-dose C1-esterase inhibitor administration on systemic inflammatory response and survival in patients with sepsis and demonstrated that high-dose C1-esterase inhibitor infusion down-regulated the systemic inflammatory response and was associated with improved survival rates in sepsis patients ¹³³ .
The effects of interferon-gamma on sepsis-induced immunoparalysis	NCT01649921 Recruiting	A decrease in monocyte function can be seen in sepsis and may predispose patients to infections. Interferon (IFN)-gamma can restore monocytic function ¹³⁵ . The primary aim of this study is to assess the effects of adjunctive therapy with IFN-gamma on immune function in patients with septic shock in a placebo-controlled manner. Moreover, the investigators want to evaluate new markers that could be used to identify patients with immunoparalysis, and to monitor the patient's immunological response to IFN-gamma.
Does GM-CSF Restore Neutrophil Phagocytosis in Critical Illness? (GMCSF)	NCT01653665 Recruiting	GM-CSF has been studied for use in sepsis in several small trials with conflicting results ¹⁰ . The putative role for GM-CSF in sepsis is to restore the ability of neutrophils to ingest and kill bacteria. Future larger scale clinical trials are needed.
Impact of Low Dose Unfractionated Heparin Treatment on Inflammation in Sepsis	NCT02135770 Recruiting	Heparin compounds have anti-inflammatory and anti-thrombotic effects that may be beneficial for the treatment of sepsis. Two prior trials have demonstrated conflicting results ^{138,140} . This study enrolls up to 100 patients to assess the effects of unfractionated heparin on inflammatory markers as well as mortality and improvement in APACHE II score.

Trial Name	Identifier and Status	Description
Statin Therapy in the Treatment of Sepsis	NCT00676897 Recruiting	Statins have anti-inflammatory properties including the ability to suppress endotoxin-induced up-regulation of TLR-2 and TLR-4. Small studies have yielded conflicting results and this study is a small randomized, double-blind trial assessing the outcome of time to shock reversal as well as IL-6 levels.
Role of 'Pentoxifylline and or IgM Enriched Intravenous Immunoglobulin in the Treatment of Neonatal Sepsis	NCT01006499 Status unknown	Pentoxifylline inhibits neutrophil adhesion and activation and modulates cytokine production in response to endotoxin. An early study ¹⁴² demonstrated benefit in illness severity scores but no improvement in mortality. This study aims to assess pentoxifylline effects in neonates with sepsis with or without IgM enriched immunoglobulin.
Esmolol Effects on Heart and Inflammation in Septic Shock (ESMOSEPSIS) Pilot Phase II Study: Hemodynamic Tolerance and Anti-inflammatory Effects of Esmolol During the Treatment of Septic Shock (THANE)	NCT02068287 Recruiting NCT02120404 Not yet open	Beta-adrenergic system over-activity is common in sepsis and may contribute to poor outcomes. An early study demonstrated benefits of esmolol on hemodynamic parameters in septic patients ¹⁴³ . These studies assess the hemodynamic effects of esmolol as well as changes in microcirculation and cytokine profiles in patients with sepsis.
Dexmedetomidine for Sepsis in ICU Randomized Evaluation Trial (DESIRE) The Effect of Dexmedetomidine on Microcirculation in Severe Sepsis Safety Study of Dexmedetomidine in Septic Patients	NCT01760967 Recruiting NCT02109965 Not yet open NCT01976754 Recruiting	Dexmedetomidine (DEX) is a selective agonist of the α_2 -adrenergic receptors that suppresses inflammatory mediators in animal models of sepsis ¹⁴⁴ . These trials are testing the hypothesis that DEX may improve clinical outcomes and have organ protective effects in patients with sepsis.
Acetaminophen for the Reduction of Oxidative Injury in Severe Sepsis (ACROSS)	NCT01739361 Completed	Cell-free hemoglobin is present in the plasma of patients with sepsis and is associated with poor outcomes ¹⁴⁵ . Acetaminophen may have a protective effect by inhibiting hemoprotein-mediated lipid peroxidation. This study aims to assess systemic markers of oxidative stress and lipid peroxidation in septic patients and the effects of acetaminophen on these compounds.
Selenium Replacement and Serum Selenium Level in Severe Sepsis and Septic Shock Patients (SEREAL)	NCT01601938 Not yet Recruiting	Patients with sepsis have been found to have low selenium levels ¹⁴⁶ . In some studies, high-dose selenium has shown benefit ^{146,147} . This study will be performed to determine whether selenium replacement reduces 28-day mortality of severe sepsis and septic shock patients, and to investigate whether selenium replacement contributes differently to the mortality reduction of the patients according to their initial serum selenium level.
Citrulline in Severe Sepsis	NCT01474863 Recruiting	Low levels of citrulline are associated with an increased risk of acute respiratory distress syndrome and this may be due to citrulline overconsumption due to nitric acid production ¹⁴⁸ . This is a randomized, double-blind, placebo-controlled, phase 2 study to evaluate biochemical, clinical, and safety effects of 2 doses of intravenous L-citrulline compared to placebo in patients with severe sepsis at risk for or with acute lung injury. The hypothesis is that intravenous L-citrulline will decrease the development or progression of acute lung injury in patients with severe sepsis compared to placebo.
Rapid Administration of Carnitine in sEpsis (RACE)	NCT01665092 Recruiting	Exogenous L-carnitine administration enhances glucose and lactate oxidation, attenuates fatty acid toxicity, and improves cardiac mechanical efficiency ¹⁴⁹ . The overall goal of this proposal is to investigate L-carnitine as a novel adjunctive treatment of septic shock. The primary hypothesis is: Early adjunctive L-carnitine administration in vasopressor dependent septic shock will significantly reduce cumulative organ failure at 48 hours with an associated decrease in 28-day mortality suggesting the need for further phase III study
Zinc Therapy in Critical Illness The Impact of Zinc Supplementation on Innate Immunity and Patient Safety in Sepsis	NCT01162109 Recruiting NCT02130388	Zinc is essential for normal immune function, oxidative stress response, and wound healing. Zinc deficiency leads to loss of innate and adaptive immunity and increased susceptibility to infections. There is strong biologic rationale to suggest that the zinc deficiency seen in nearly all sepsis patients may contribute to the development of sepsis syndrome and to the "immunoparalysis" common in sepsis patients ^{118,147} . This study has three specific aims, 1) to perform a phase I dose-finding study of intravenous zinc in mechanically ventilated patients with severe sepsis; 2) to define the pharmacokinetic of intravenous zinc in mechanically ventilated patients with severe sepsis compared to healthy controls; and 3) to investigate the impact of zinc on inflammation, immunity, and oxidant defense in patients with severe sepsis.

Trial Name	Identifier and Status	Description
		This study will determine if zinc supplementation is safe to use in patients with severe sepsis or septic shock. This study will also gather preliminary information to evaluate the impact that zinc has on the immune system
ADJunctive coRtICosteroid trEatment iN criticAlly iL Patients With Septic Shock (ADRENAL) Efficacy of Hydrocortisone in Treatment of Severe Sepsis/ Septic Shock Patients With Acute Lung Injury/Acute Respiratory Distress Syndrome (ARDS)	NCT01448109 Recruiting NCT01284452 Recruiting	Corticosteroids (hydrocortisone) are sometimes administered to patients with sepsis. ^{150,151} Previous research has suggested that the use of low dose steroid may have short-term benefits in improving the circulation. However, there is no agreement about whether treatment with or without low dose steroids improves the overall recovery and survival in patients with septic shock. This is a large study in 3800 patients who will be randomized to receive either hydrocortisone 200mg or placebo daily for 7 days as a continuous intravenous infusion while in intensive care. The patient will be followed for 90 days. This study will investigate whether hydrocortisone can effectively prevent disease progression and death in severe sepsis/septic shock patients who also have acute lung injury, or acute respiratory distress syndrome
Efficacy of Melatonin in Patients With Severe Sepsis or Septic Shock	NCT01858909 Not yet Recruiting	Melatonin's protective action against sepsis is suggested to be due to its antioxidant, immunomodulating and inhibitory actions against the production and activation of pro-inflammatory mediators ¹⁵² . However, melatonin has not been studied in human sepsis. This placebo-controlled trial will evaluate the survival to 28 days as well as other outcomes measures and biochemical and cytokine profiles.
Cholecalciferol Supplementation for Sepsis in the ICU (CSI)	NCT01896544 Recruiting	Vitamin D has been identified as a key regulator of the immune system ¹⁵³ . Little is known about the effects of vitamin D supplementation in patients with severe infections. This study will investigate whether high doses of cholecalciferol (vitamin D3) can improve vitamin D status and boost certain aspects of the immune system in patients with sepsis.
Thiamine as a Metabolic Resuscitator in Septic Shock	NCT01070810 Recruiting	Thiamine deficiency is common in patients with sepsis and is associated with an increase in mortality. The goal of this study is determine whether the use of thiamine in patients with septic shock will result in attenuation of lactic acidosis and a more rapid reversal of shock.
Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI)	NCT02106975 Not yet open (May 2014)	Characteristics of severe sepsis include ascorbate (reduced vitamin C) depletion and parenteral administration of ascorbate decreases hypotension, edema, multiorgan failure, and death in animal models of sepsis ¹⁵⁵ . Goal of this study is to determine if vitamin C can attenuate lung injury, organ failure and inflammation in sepsis.