

RESEARCH REVIEW

Surgical Sepsis and Organ Crosstalk: The Role of the Kidney

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Submitted for publication September 17, 2010

Acute kidney injury (AKI) is a common complication of hospitalized patients, and clinical outcomes remain poor despite advances in renal replacement therapy. The accepted pathophysiology of AKI in the setting of sepsis has evolved from one of simple decreased renal blood flow to one that involves a more complex interaction of intra-glomerular microcirculatory vasodilation combined with the local release of inflammatory mediators and apoptosis. Evidence from preclinical AKI models suggests that crosstalk occurs between kidneys and other organ systems via soluble and cellular inflammatory mediators and that this involves both the innate and adaptive immune systems. These interactions are reflected by genomic changes and abnormal rates of cellular apoptosis in distant organs including the lungs, heart, gut, liver, and central nervous system. The purpose of this article is to review the influence of AKI, particularly sepsis-associated AKI, on inter-organ crosstalk in the context of systemic inflammation and multiple organ failure (MOF). © 2011 Elsevier Inc. All rights reserved.

Key Words: acute kidney injury; sepsis; inflammation; apoptosis; immune response.

INTRODUCTION

Acute kidney injury (AKI) is a common and often catastrophic complication amongst hospitalized patients. It affects 3% to 7% of patients admitted to the hospital and approximately 25% to 30% of patients in the intensive care unit (ICU) [1]. Mortality rates for ICU patients with AKI have a reported range from 30% to 70% even

with advances in renal replacement therapy, and AKI is an independent risk factor for mortality even after adjustment for demographics, severity of illness and other patient factors [2, 3]. AKI has been summarized by two consensus definitions: (1) The Risk-Injury-Failure-Loss-End stage renal disease (RIFLE) classification, and (2) The Acute Kidney Injury Network (AKIN) criteria. The RIFLE classification uses serum creatinine or glomerular filtration rate (GFR) and urine flow per body weight over time to stratify renal injury by severity, with “risk” as the least severe category and “failure” as the most severe category. The AKIN classification modified the RIFLE criteria in 2007 to exclude GFR and classify AKI into stages 1–3, with stage 3 representing the requirement for renal replacement therapy [4].

Despite the advancement in renal replacement therapy, the mortality rates associated with AKI have remained unchanged over the past 2 decades [3]. Both clinical and translational laboratory studies have demonstrated very complex mechanisms of interactions between the injured kidney and distant organs such as the lung, heart, liver, gut, brain, and hematologic system. Recent studies on AKI-associated distant organ dysfunction have highlighted the importance of both the innate and adaptive immune response, activation of proinflammatory cascades, and an alteration in transcriptional events during ischemic AKI. For example, cell adhesion molecule and cytokine-chemokine expression, apoptosis dysregulation, and leukocyte trafficking to distant organs all occur during ischemic AKI. The goal of this article is to review emerging concepts regarding the clinical significance of sepsis-associated AKI, the altered immune response that follows, and the mechanisms by which AKI contributes to distant organ injury. For a complete list of abbreviations used in this manuscript, please see Table 1.

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TABLE 1
Abbreviations

ACCP/SCCM	American College of Chest Physicians/Society of Critical Care Medicine
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALI	Acute lung injury
APC	Activated protein C
ARDS	Acute respiratory distress syndrome
ARDSNet	Acute Respiratory Syndrome Clinical Trials Network
BNx	Bilateral nephrectomy
CHIF	Channel inducing factor
CO	Cardiac output
DIC	Disseminated intravascular coagulation
GFAP	Glial fibrillary acidic protein
GFR	Glomerular filtration rate
GM-CSF	Granulocyte macrophage colony-stimulating factor
HSC	Hepatic stellate cells
ICAM	Inter-cellular adhesion molecule
ICU	Intensive care unit
IIT	Intensive insulin therapy
IL	Interleukin
INF- γ	Interferon-gamma
iNOS	Inducible nitric oxide synthase
IRI	Ischemia reperfusion injury
KC	Keratinocyte chemoattractant
LPS	Lipopolysaccharide
LV	Left ventricle
M2AA	Methyl-2-acetamidoacrylate
MIP-2	Macrophage inflammatory protein-2
MOF	Multiple organ failure
NF- $\kappa\beta$	Nuclear factor $\kappa\beta$
NSQIP	National Surgical Quality Improvement Project
PEEP	Positive end-expiratory pressure
PECARD	Program to improve care in acute renal disease
RBF	Renal blood flow
RIFLE	Risk injury failure loss end stage renal disease
RRT	Renal replacement therapy
Saa3	Serum amyloid A 3
SIRS	Systemic inflammatory response syndrome
SOAP	Sepsis occurrence in acutely ill patients
Th	T helper cell
TNF- α	Tumor necrosis factor alpha

SURGICAL SEPSIS AND ITS ROLE IN AKI

Sepsis is a well-established risk factor for AKI, and mortality rates in patients with both AKI and sepsis are much greater than the mortality rate in patients with either AKI or sepsis alone, particularly in the setting of multiple organ failure (MOF) [5]. Thus, the combination of sepsis and AKI poses a particularly serious problem and the concept that sepsis-associated AKI may have a distinct pathophysiology from other etiologies of AKI is supported not only by experimental data and evidence from small clinical studies, but also by epidemiologic data showing “dose response” trends in incidence rates and outcomes for septic AKI by severity of either sepsis or AKI [5–11] (Fig. 1).

While the etiology of AKI in critically ill patients is multifactorial, sepsis has consistently been a leading

contributing factor for AKI in the ICU setting [12–16]. The Centers for Disease Control has listed sepsis as the 10th leading cause of death, and annual costs due to this disease exceed \$17 billion [17]. The National Surgical Quality Improvement Project (NSQIP) dataset from the American College of Surgeons defines sepsis as the presence of systemic inflammatory response syndrome (SIRS) with a source of infection, as documented by positive blood cultures or purulence from any site thought to be causative [18]. Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Guidelines [19]. Severe sepsis is not separately identified by NSQIP data but is included in the definition of septic shock and sepsis with organ and/or circulatory dysfunction (Table 2) [20, 21].

Surgical sepsis, defined as sepsis requiring surgical intervention for source control or sepsis within 14 d of a surgical procedure, occurs more frequently than other postoperative complications such as pulmonary embolism and myocardial infarction [18, 21]. The published incidence rate of surgical sepsis is three cases per 1000 patients, and it carries a high mortality rate ranging from 26% to 50% [16]. The prevalence of AKI in patients with severe sepsis or septic shock has been reported as high as 43% [14]. While the epidemiology of surgical sepsis-associated AKI is largely unknown, prior studies describing sepsis-associated AKI have consistently concluded that it contributes to nearly 2-fold higher mortality than either nonseptic AKI or sepsis alone [12–16]. This is likely due to the fact that AKI rarely occurs in isolation and is associated with distant organ dysfunction in the context of MOF.

Surgical sepsis is considered different from medical sepsis for several reasons. First, surgical trauma and anesthetic agents used during surgery alter host local and systemic immune function. Surgical trauma systemically activates macrophages, neutrophils, natural killer cells, and endothelial cells of the innate immune response, which then in turn synthesize mediators including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). The adaptive immune response is also activated, mediated by proinflammatory type-1 helper cells (Th1) and anti-inflammatory type-2 helper cells (Th2) [22]. Additionally, in contrast to the medical ICU population, patients who have surgical sepsis often require source control in the form of urgent surgical intervention. The timing of source control must be coordinated with resuscitation efforts but has the potential to dramatically reverse the cycle of septic shock. Patients with surgical sepsis who are at highest risk for AKI are those whose clinical instability requires aggressive volume resuscitation and hemodynamic support with

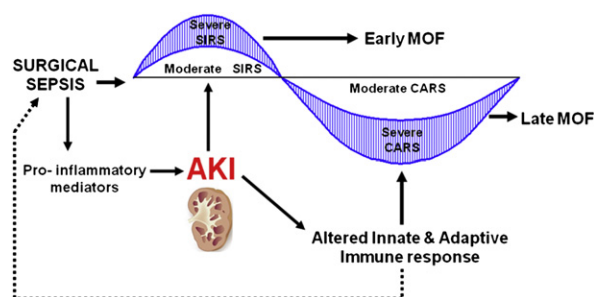


FIG. 1. Surgical sepsis and multiple organ failure—The role of the kidney. Surgical sepsis causes AKI, which in turn contributes to early SIRS and MOF, then late compensatory anti-inflammatory response syndrome (CARS) and MOF through an altered innate and adaptive immune response. (Color version of figure is available online.)

broad spectrum antimicrobial coverage prior to operative intervention. The appropriate timing of source control is unknown, however, expert consensus opinion recommends this should be completed within 6 h to break the cycle of persistent septic shock [23].

Traditional concepts of sepsis-associated AKI

The pathophysiology of sepsis-associated AKI is complex and multifactorial. Traditionally, AKI in sepsis

and septic shock was thought to result from renal ischemia secondary to vasoconstriction and inadequate renal blood flow (RBF). Some of the major mechanisms that have also been linked either directly or indirectly to sepsis-associated AKI include: (1) alterations in hemodynamics with subsequent renal vasoconstriction leading to ischemia and tissue hypoxia, (2) hyperglycemia causing functional alterations in leukocytes and macrophages leading to inflammation, and (3) activation of the coagulation and fibrinolytic cascades leading to disseminated intravascular coagulation (DIC) and microvascular thrombosis [11, 24].

Changing Paradigm in the Pathophysiology of Sepsis-Associated AKI

Our understanding of sepsis-associated AKI pathophysiology is shifting from renal vasoconstriction, ischemia, and acute tubular necrosis to that of heterogeneous vasodilation, hyperemia, and acute tubular apoptosis. The concept of renal vasoconstriction and kidney ischemia as a key pathogenic factor is certainly valid for all low-flow states (i.e., cardiogenic or hemorrhagic shock). However, during hyperdynamic states (i.e., sepsis and other acute systemic inflammatory conditions), the

TABLE 2
Sepsis and Related Definitions

Systemic inflammatory response syndrome (SIRS)	The systemic inflammatory response to a <i>variety</i> of severe clinical insults. Response includes two or more of the following clinical conditions: • Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$ • Heart rate >90 beats per min • Respiratory rate >20 breaths per min or $\text{PaCO}_2 <32$ mm Hg • White blood cell count $>12,000/\text{cu mm}$, $<4000/\text{cu mm}$ or $>10\%$ immature (band) forms.
Sepsis	The systemic response to <i>infection</i> , manifested by two or more of the above clinical criteria listed under SIRS
Severe sepsis	Sepsis associated with an acute organ dysfunction: • Neurologic: GCS¹ <13 upon recognition of sepsis or deteriorating to <13 during the first 24 h of sepsis • Pulmonary: $\text{P}_a\text{O}_2/\text{FiO}_2$ ratio <250 (<200 if lung is primary source of infection) and PCWP² (if available) not suggestive of fluid overload • Renal: One of the following: (1) $\text{UOP}^3 <0.5$ mL/kg for ≥ 1 h despite adequate volume resuscitation, (2) Increase in serum creatinine ≥ 0.5 mg/dL from baseline (measured within 24 h of starting sepsis resuscitation) despite adequate volume resuscitation, (3) increase in serum creatinine ≥ 0.5 mg/dL during the first 24 h despite adequate volume resuscitation⁴ • Coagulation: One of the following: (1) $\text{INR} >1.5$, (2) Platelet count $<80,000$ or $\geq 50\%$ decrease platelet count in 24-h period in the absence of chronic liver disease • Hypoperfusion: Lactate level >4 mmol/L
Septic shock	Sepsis-induced hypotension despite adequate volume resuscitation along with the presence of perfusion abnormalities (as above); patients requiring inotropic or vasopressor medications may not be hypotensive at the time when perfusion abnormalities are measured.
Sepsis-induced hypotension	Systolic blood pressure <90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes of hypotension.

GCS = Glasgow coma score; PCWP = pulmonary capillary wedge pressure; UOP = urine output.

Adequate volume resuscitation defined by a minimum intravenous fluid infusion of 20 mL/kg/ideal body weight or central venous pressure ≥ 8 mm Hg or PCWP ≥ 12 mm Hg.

hemodynamic alterations within the kidney appear to be heterogeneous, with reduced perfusion to microvascular beds despite increased total RBF [25]. Human data on renal hemodynamics in sepsis is limited, but a recent systematic review of the available experimental evidence showed that in all three human studies and in 30% of animal studies, RBF remained unchanged or even increased. Cardiac output (CO) was found to be the only statistically significant predictor of RBF. Furthermore, the majority of studies reporting a reduction in renal blood flow were derived mostly from hypodynamic models characterized by a reduced cardiac output. In multiple experimental models in which hyperdynamic sepsis was produced, RBF increased proportionately to CO. Therefore, it is likely that the AKI associated with sepsis occurs in a setting of normal or even raised RBF resulting in a hyperemic kidney [25–27].

The loss of GFR can now be explained by the differences in the glomerular capillary pressure created by the afferent and efferent renal vessels. In this condition, there is disproportionate increase in renal vasodilation in the efferent blood vessels as compared with the afferent vessels. This causes a reduction in glomerular capillary pressure, in turn, leading to a reduced GFR and causing oliguria and reduced solute clearance. This hypothesis was confirmed with animal models of hyperdynamic sepsis in which angiotensin II, a vasoconstrictor hormone, which causes a preferential increase in efferent arteriole resistance, was administered by continuous infusion. The animals, which received the infusion, demonstrated a restored arterial blood pressure and a significantly increased urine output and creatinine clearance compared with placebo [28]. Thus, it seems that sepsis-associated AKI does not result from ischemia secondary to decreased overall renal blood flow but instead from derangements inside the glomerulus leading to decreased GFR.

Though sepsis-associated AKI may result from heterogeneous hypoperfusion as opposed to global renal hypoperfusion, similar injury patterns are demonstrated in experimental models of both sepsis and ischemia-reperfusion injury (IRI) induced AKI. In addition to intra-glomerular vascular changes, nonhemodynamic effects of sepsis-associated AKI are locally mediated by the release of inflammatory cytokines, particularly $\text{TNF-}\alpha$, with subsequent tubular cell apoptosis [29]. Studies have shown that endotoxin stimulates the release of $\text{TNF-}\alpha$ from glomerular mesangial cells [30]. Additional work has demonstrated attenuation of $\text{TNF-}\alpha$ mediated acute renal failure in both TNF receptor-neutralized and in TNF receptor knockout mice [31, 32]. Cellular apoptosis, which is an energy-requiring and genetically-directed process, has been demonstrated to occur alongside necrosis in experimental models of both ischemia-reperfusion and septic

acute kidney injury. Apoptosis was elicited in cultured kidney proximal tubular and glomerular cells by both $\text{TNF-}\alpha$ and lipopolysaccharide (LPS) [33, 34]. Caspases, enzymes responsible for carrying out apoptosis, are inhibited in animal models of both LPS-induced sepsis and kidney IRI, and in this setting, mice treated with caspase inhibitors are protected from both sepsis and IRI associated AKI [35, 36].

Hyperglycemia and DIC commonly occur in patients with sepsis and MOF, and therapies including intensive insulin therapy (IIT) and activated protein C (APC) decrease both the onset of sepsis-associated AKI and mortality [11, 37]. The benefits of IIT are most profound in patients with surgical sepsis, and a number of physiologic mechanisms of renal protection have been proposed [38]. Despite a lack of influence on hemodynamics, IIT improves the lipid profile in patients with sepsis and MOF, and attenuation of both ischemic and endotoxemic AKI by high density lipoprotein has been demonstrated in experimental models [39–41]. AKI and hyperglycemia are also associated with an increase in expression of inducible nitric oxide synthase (iNOS), endothelial activation of ICAM-1, upregulation of proinflammatory cytokines ($\text{TNF-}\alpha$, IL-6), release of oxidative stress mediators and infiltration of inflammatory cells, which lead to renal tubular injury [38, 42, 43]. Additionally, APC has anti-inflammatory, antithrombotic and profibrinolytic properties and reduces mortality in severe sepsis [37]. In a model of polymicrobial sepsis induced by cecal ligation and puncture, APC administration decreased the expression of inflammatory cytokines, the incidence of apoptosis, and the presence of acute tubular necrosis [44].

In summary, AKI associated with sepsis can be characterized by a vasomotor nephropathy, which includes disturbances in renal microcirculation, activation of proinflammatory mediators, and activation of renal cell apoptosis, thus resulting in kidney failure and imbalances in body water and electrolyte homeostasis. Due to the difficulties associated with measuring these effects simultaneously and the complexity of the condition, further studies will be needed to elucidate the detailed mechanisms of sepsis-associated AKI and the pathway for recovery of kidney function after injury.

KIDNEY CROSSTALK WITH DISTANT ORGANS

The incidence of AKI continues to increase and is associated with a changing spectrum of illnesses, significant comorbid and extra-renal complications, and unsatisfactory preventive or treatment strategies [45–47]. Despite advances in treatment such as renal replacement therapy, mortality rates associated with AKI have not changed significantly since the 1950s [2, 3]. This is likely

due to the fact that AKI rarely occurs in isolation and is usually a component of inter-organ crosstalk and MOF. It is apparent that much of the increased risk of death is derived from extra-renal complications related to remote organ damage and dysfunction. More recently, animal studies have shown a direct effect of AKI on distant organs such as the lung, brain, liver, and the gut [48–53]. These animal studies include models of IRI and sepsis, namely LPS endotoxin-induced sepsis, due to its reproducibility in creating distant organ failure including AKI [54].

Kidney-Lung Interactions During AKI

Currently, the kidney and lung represent the two most commonly involved organs in MOF [55]. Acute lung injury (ALI) is defined by the American-European Consensus Conference on Acute Respiratory Distress Syndrome (ARDS) as a P_aO_2/FiO_2 ratio of less than 300 and chest radiograph findings of acute bilateral infiltrates in the absence of elevated cardiac filling pressures [56]. Acute hypoxia is a frequent presenting symptom of postoperative sepsis, and a decreased P_aO_2/FiO_2 ratio results from increased pulmonary shunting in response to acidosis and carbon monoxide retention. ALI accounts for a significant component of the mortality associated with AKI even in the absence of volume overload contributed by renal failure [57–59]. The mortality of combined AKI and ALI is extremely high and may approach 80% [60]. Therefore, defining the mechanisms of kidney-lung crosstalk in the critically ill is necessary for reducing overall mortality associated with AKI.

Mechanisms of Kidney-Lung Crosstalk

The mechanisms of AKI-associated lung injury remain incompletely understood. Several studies have demonstrated the involvement of proinflammatory and proapoptotic factors such as leukocyte trafficking, cytokines/chemokines, activation of caspases, oxidative stress, and uremic toxins. AKI and ALI act as a self-propagating cycle (Fig. 2). AKI leads to lung injury and inflammation and in turn, ALI, with its attendant hypoxemia and hypercapnia worsened by mechanical ventilation-associated high positive-end expiratory pressure (PEEP), causes a decline in renal hemodynamics and function. Experimental evidence has demonstrated that lung injury in the setting of AKI is featured by marked pulmonary microvascular permeability, erythrocyte sludging in lung capillaries, interstitial edema, focal alveolar hemorrhage and inflammatory cell infiltration [49, 52, 59]. Kidney IRI has been shown not only to cause an increase in pulmonary vascular permeability, but it also results in down-regulation of the pulmonary epithelial salt and water

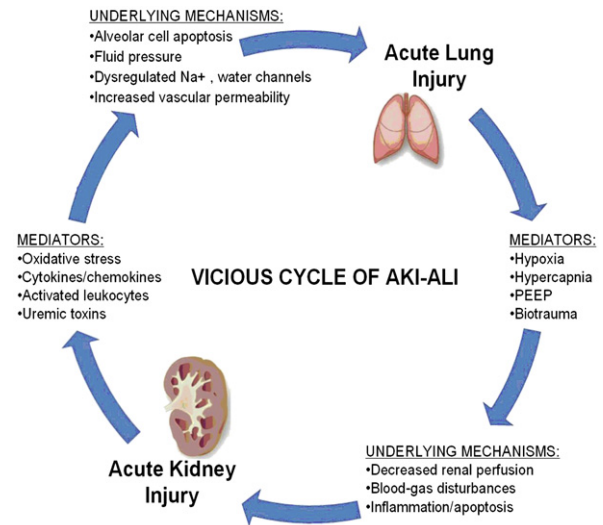


FIG. 2. Vicious cycle of AKI and ALI. AKI induces pathophysiologic effects on the lung *via* cellular and soluble mediators. ALI, in turn, facilitates and exacerbates kidney dysfunction *via* metabolic and biochemical derangements. (Color version of figure is available online.)

transporters (ENaC, Na, K-ATPase, and aquaporins) in the rat lung, all of which contribute to decreased alveolar fluid clearance [49, 59, 61].

Role of Inflammation, Cytokines, and Chemokines

The upregulation of proinflammatory genes and inflammatory cytokines are important mediators connecting the effects of AKI on distant organs [62]. Recent studies by Hassoun and colleagues investigated the lung structural, functional and genomic response during kidney IRI or bilateral nephrectomy (BNx) [52, 63]. A comprehensive genomic map and analysis of inflammation-associated transcriptional changes in local and remote organs during ischemic AKI identified markedly similar transcriptomic changes occurring concomitantly in both the kidney and lung during AKI, including significant changes in the expression of 109 prominent proinflammatory genes including Cd14, serum amyloid A 3 (Saa3), lipocalin 2, CXCL-2, and the IL-1 receptor (IL-1r2) [63]. Of note, the demonstrated changes in the lung following ischemic AKI were distinguishable from those caused by uremia alone and involved early and persistent activation of proinflammatory and proapoptotic pathways [52].

Cytokines/chemokines have a key role in the initiation as well as progression of both AKI and ALI. Interleukin-6 (IL-6), interleukin-10 (IL-10), and Saa3 are increased in the lung during AKI [59, 64]. Klein *et al.* demonstrated that IL-6 is elevated after both ischemic AKI and BNx in mice and in the serum of patients with AKI, and furthermore predicts mortality [61]. The same investigators also discovered that

IL-6-deficiency reduced lung neutrophil infiltration, myeloperoxidase activity, expression of the chemokines KC (CXCL-1) and MIP-2 (macrophage inflammatory protein-2), and capillary leak during AKI in mice. Another recent study has demonstrated cytokine-mediated pulmonary injury during AKI, including increased IL-6, IL-1, IL-12 (p40), granulocyte macrophage colony-stimulating factor (GM-CSF), whereby anti-inflammatory IL-10 inhibits both production and action of numerous proinflammatory cytokines and reduced lung injury during AKI [53, 61]. Clearly, the mechanisms by which inflammation might initiate and affect AKI-induced ALI are complex and only partially understood but may be influenced by regulation of cytokines and chemokines.

Lung Apoptosis

There is increasing evidence that pulmonary cell apoptosis may play an important role in the pathophysiology of AKI induced ALI [65]. Both enhanced pulmonary endothelial and epithelial cell apoptosis and delayed leukocyte apoptosis have been associated with ALI [66–68]. Investigations of vascular permeability have highlighted the importance of the balance between complex tethering forces involved in cell-to-cell and cell-to-extracellular matrix interactions. These studies have also shown that endothelial apoptosis leads to the disruption of these complex interactions and a potential for loss of endothelial barrier function [69]. Recent laboratory data demonstrated that kidney IRI in rats induces pulmonary endothelial apoptosis and lung injury, and these effects were abrogated by the caspase inhibitor z-VAD-fmk, suggesting a direct role of caspase dependent apoptosis in ischemic AKI induced lung injury [70].

Role of Innate and Adaptive Immunity

Kidney ischemia-reperfusion injury activates both the innate and adaptive immune responses [71]. The innate immune response includes neutrophils, macrophages, and possibly natural killer cells. The adaptive immune system is also activated after kidney IRI via CD4⁺ T cells, particularly of the Th1 phenotype [71]. Pathogenesis of postischemic injury is thought to be mediated by interferon- γ (INF- γ) produced by CD4⁺ T cells [72]. Additionally, the inactivation of IL-16, a chemottractant strongly expressed on renal tubules during IRI, resulted in less IRI-induced CD4⁺ lymphocyte trafficking and subsequent kidney injury and dysfunction [73]. T lymphocyte trafficking occurs as early as 1 h after kidney IRI and persists for up to 6 wk postinjury [74, 75]. In fact, these T cells may recognize antigens released during kidney IRI and subsequently target the kidney in an autoimmune response, leading

to long-term progression of renal dysfunction. This mechanism was demonstrated in a murine adoptive transfer model in which naïve mice received T cells from mice who were 6 wk post-kidney IRI and subsequently developed increased albuminuria [74].

Leukocytes play a fundamental role in the development of ALI/ARDS and several recent studies have documented lung leukocyte activation and trafficking during experimental AKI. In rat models of both bilateral kidney IRI and bilateral nephrectomy, studies have shown early and sustained lung neutrophil sequestration [53, 76]. While neutrophils are the key mediators in several extra-pulmonary models of ALI such as sepsis and mesenteric IRI, their importance in AKI-associated lung injury is less clear, and in fact, uremic neutrophils have been shown to attenuate ALI in mice [51].

Macrophage and lymphocyte infiltration and/or proliferation are other potential mediators of the distant organ effects of AKI. Macrophage activation inhibitor CNI-1493 has been shown to attenuate lung microvascular leak following bilateral kidney IRI in rats [49]. In addition, unilateral kidney ischemia has resulted in increased macrophages in both the contralateral kidney as well as the cardiac interstitium [77]. Lie *et al.* have recently reported on the infiltration of activated CD3⁺ CD8⁺ cytotoxic T lymphocytes into mouse lungs during kidney IRI and their potential role in mediating lung apoptosis in this setting [78].

Kidney Interactions With Other Distant Organs

Acute kidney injury interacts with and affects many other major organ-systems including the heart, brain and central nervous system, the hematologic system, the liver, and gut [79]. Though the exact pathophysiology of these interactions are unclear, the general mechanisms by which AKI induces distant organ effects remain fairly universal and include inflammation, activation of both soluble and cellular factors, as well as hemodynamic and neurohumoral alterations which lead to cellular apoptosis and organ damage (Fig. 3).

Kidney-Heart Interactions

While cardiovascular collapse is one of the most common causes for death in the setting of AKI, the mechanisms involved are incompletely understood [80]. It has been demonstrated by Kelly *et al.* that during kidney IRI in rats there is left ventricular (LV) dilatation, increased left ventricular end diastolic and end systolic diameter, increased relaxation time, and decreased fractional shortening [48]. It has also been shown that cardiac ischemia, in a setting of AKI, causes a sustained ventricular fibrillation of longer duration than cardiac ischemia without AKI [81]. Conversely, some studies

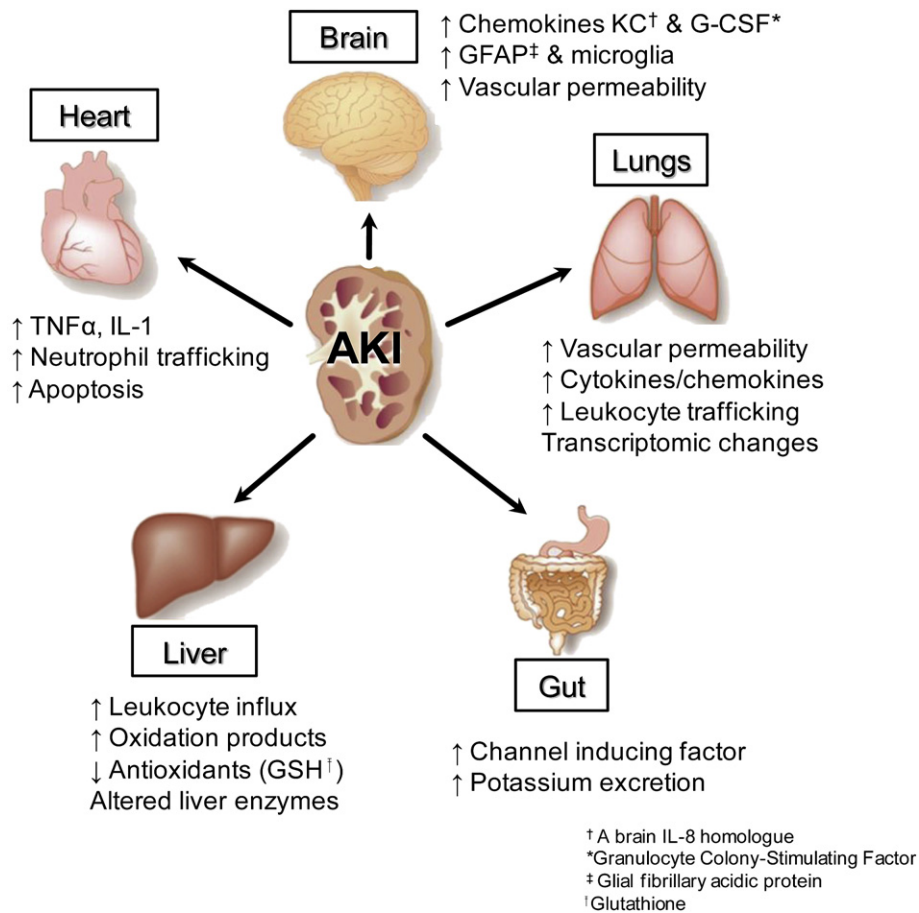


FIG. 3. Acute kidney injury and its effects on major organ-systems in the body. AKI manifests distant organ injury in the heart, brain, lungs, liver, and gut in a variety of mechanisms, including increased expression of soluble proinflammatory mediators, innate and adaptive immunity, cellular apoptosis, physiologic derangements, and genomic changes. (Color version of figure is available online.)

have shown that ischemic preconditioning of the kidney can induce distant organ protection in certain circumstances, protecting the myocardium against irreversible damage produced by prolonged coronary artery occlusion under hypothermic conditions [47].

Cardiac myocyte apoptosis and neutrophil infiltration are two of the most important contributors to the pathophysiology of myocardial infarction during AKI and transgenic models have demonstrated that even apoptosis alone can lead to lethal heart failure [5, 31, 77, 78, 82]. During AKI, there is an increased amount of both cardiac and systemic TNF- α and IL-1 along with increased expression of ICAM-1 mRNA, which results in myocyte apoptosis and neutrophil infiltration of the heart [48, 83]. Decreased renal ischemia time attenuates cardiac apoptosis and IL-1 and ICAM-1 levels, as does administration of anti-TNF- α antibodies [48].

Kidney-Brain Interactions

Effects of AKI on brain and nervous system include early clinical signs such as clumsiness, fatigue,

impaired concentration, and apathy that may later progress to delirium, confusion, and coma. Interestingly, dialysis improves but fails to fully correct, central nervous system manifestations of renal failure in both the acute and chronic setting [84]. Much of the symptoms of encephalopathy are attributed to uremic toxins, however, both soluble and cellular inflammatory mediators, similar to those seen in kidney-lung and kidney-heart interactions, have also been implicated.

It has been demonstrated that AKI causes an increase in the levels of soluble mediators such as KC, G-CSF, and GFAP in the cerebral cortex and hippocampus of the brain, which may function to recruit neutrophils to sites of neuronal damage. This increased KC and G-CSF in the brain potentially represent increased neuronal production of these proinflammatory factors or an accumulation of these proteins through an altered blood-brain barrier (increased microvascular permeability) arising from a systemic or renal source. AKI also causes a cell-mediated inflammatory response in the brain such as seen with activated microglial cells (brain macrophages) [85].

Kidney-Liver Interactions

Liver injury often correlates with severity of kidney injury. Ischemic AKI has been shown to induce oxidative stress and promote inflammation, apoptosis, and tissue damage in hepatocytes. Hepatic stellate cells (HSCs) are known to regulate leukocyte trafficking and activation by secreting chemokines such as interleukin-8 (IL-8) [86]. Crosstalk between CD40-expressing HSCs and immune effector cells likely occurs through activating nuclear factor $\kappa\beta$ (NF- $\kappa\beta$) and c-Jun N-terminal kinase to upregulate chemokine secretion [87]. These HSCs are LPS-inducible, and LPS endotoxemia causes hepatic injury by enhancing neutrophil transmigration out of the hepatic sinusoid and into the liver parenchyma [88].

During ischemic and nonischemic AKI, oxidative stress causes hepatic malondialdehyde, an index of lipid peroxidation, to increase while total glutathione (a antioxidant) decreases [89]. Oxidative stress occurs as a component of the surgical stress response, particularly after IRI, sepsis, kidney, and liver failure [90–92]. Oxidative stress also plays an important role in sepsis-associated AKI. In an animal model of sepsis induced by cecal ligation and puncture, the administration of antioxidants ethyl pyruvate and methyl-2-acetamidoacrylate (M2AA) significantly reduced mortality, improved the pro- and anti-inflammatory cytokine response, and attenuated liver and kidney injury [93, 94]. Kidney-liver crosstalk during AKI, therefore, likely occurs by a complex combination of soluble inflammatory mediators and cellular immunity.

Kidney-Gut Interactions

In the past, investigators and clinicians have labeled the gut as the “motor” of MOF due to its ability to amplify the systemic SIRS response in the setting of shock and gut hypoperfusion [95–97]. Mechanisms by which this crosstalk occurs include increased intestinal epithelial permeability, interactions between host and bacterial pathogens, and propagation of toxins to distant organs *via* the lymphatic system [96, 98–100]. These mechanisms could potentially play a role in the converse direction of interactions between the kidney and the gut during AKI.

Our understanding of how AKI influences gut physiology is limited, however, the gut has been shown to mitigate some adverse effects of AKI, particularly in the handling of excess potassium. Clinical studies have long demonstrated the increased secretion of potassium by the colon and rectum [101, 102]. Recent literature has linked channel-inducing factor (CHIF), a potassium channel regulator found in both the kidney and the colon, to ischemic IRI. In animals subjected to kidney IRI, CHIF was upregulated in the colon while

a renal secretory potassium channel, ROMK1, was downregulated in the kidney, possibly explaining why hyperkalemia does not universally occur in AKI [50, 103]. Aldosterone secreted from the kidney is associated with the upregulation of CHIF in the gut and may serve a role in kidney-gut crosstalk, however, much potential for research exists in elucidating the mechanisms of AKI induced gut injury [50].

CONCLUSION

AKI is a common complication in hospitalized patients, and mortality rates of AKI in conjunction with sepsis and MOF are unacceptably high. Our understanding of the pathophysiology of sepsis-associated AKI continues to evolve, as does our understanding of the mechanisms by which AKI induces distant organ failure. Further investigation of AKI-induced distant organ effects may lead to potential therapeutic targets and a future reduction in patient mortality.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health (NIH) K08HL089181.

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