Abstract:

Acute kidney injury is a common morbidity of pediatric sepsis and carries an increased risk of mortality. The pathophysiology of sepsis associated acute kidney injury was previously believed to be secondary to decreased global renal perfusion causing hypoxia-induced injury; however, newer research suggests this paradigm is overly simplistic, and injury is now considered multifactorial in origin. Mechanisms that contribute to kidney injury include alterations in microvascular renal blood flow, inflammation and changes in bioenergetics. Clinically, defining acute kidney injury has undergone recent examination and revision, with new interest in evaluating novel biomarkers which measure kidney function more accurately with greater predictive power for patient outcomes. Specific interventions to prevent sepsis associated kidney injury by emergency care practitioners and other frontline providers are currently lacking, and no significant evidence for such practices exist. With a growing understanding of the mechanisms of injury, novel therapeutic targets have been proposed, but current human studies have yet to be performed to help guide the practitioner.

Keywords:

acute kidney injury; sepsis; children; neutrophil gelatinase associated lipocalin; cystatin-C; autophagy

*Division of Critical Care, Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL; †Division of Cardiology, Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL; Reprint requests and correspondence: Geoffrey E. Mickells MD, Ann & Robert H. Lurie Children's Hospital of Chicago, Division of Critical Care Medicine, 225 E Chicago Ave., Box 73, Chicago, IL 60611.

Acute Kidney Injury in Pediatric Sepsis

Geoffrey E. Mickells, MD*, Michael-Alice Moga, MD*†, Craig M. Smith, MD*

Acute kidney injury (AKI) is an important morbidity that can develop as a result of sepsis and septic shock. In fact, AKI is often a marker of critical illness in children. The defining study for one of the most common systems for grading pediatric AKI (pediatric RIFLE—*R*isk, *I*njury, *F*ailure, *L*oss, *E*nd-stage renal disease) criteria followed 150 children admitted to a single university-based, tertiary care pediatric intensive care unit (PICU) of whom 85% developed AKI,[1] suggesting that AKI may be the rule rather than the exception in critically ill children. Studies of pediatric AKI indicate that sepsis is one of the most common causes accounting for between 15% to 27% of all cases of AKI.[2,3] Other leading causes of AKI in children include congenital heart disease and heart failure, use of nephrotoxic agents, and multiorgan dysfunction syndrome. In adults, AKI occurs in 30 and 66% of patients identified with sepsis, but such data in children are currently lacking.[4–6]

The combination of sepsis and AKI in pediatric patients is particularly serious with multiple studies showing mortality rates of 57 to 66%.[7,8] These rates are considerably higher than the mortality rates for patients with sepsis or AKI alone. Multiple studies have confirmed that AKI is an independent risk factor for death in both pediatric sepsis and the general PICU population and is associated with increased length of stay and prolonged mechanical ventilation.[1,8] A study conducted in two Canadian PICUs between 2003 and 2007 demonstrated a three-fold increase in mortality for patients with AKI. The Virtual PICU Systems database suggests that overall PICU mortality is approximately 3%[9,10] and mortality increases to nearly 10% for patients admitted with sepsis.[11] This mortality rate is further supported by an examination of the Virtual PICU Systems database from 2006 to 2008 conducted by Ghuman, Newth, and Khemani. This group

(E-mail: gmickells@luriechildrens.org (G.E. Mickells), mmoga@luriechildrens.org (M.-A. Moga), cmsmith@luriechildrens.org (C.M. Smith)

1522-8401

reported a mortality rate of 9.8% in septic children over the age of 2 years.[12] Markovitz and colleagues interrogated the Pediatric Health Information System Database for all pediatric patients (including neonates) with sepsis and discovered a mortality rate of 23%, which the authors attributed to a selection bias towards more critically ill children.[13] Taken together, these data indicate that sepsis is an important contributor to PICU mortality and AKI is an important modifier of mortality risk for septic children.

PATHOPHYSIOLOGY

The pathophysiology of AKI has long been presumed to be due to a combination of global kidney hypoperfusion and inadequate metabolic substrate delivery resulting in tissue hypoxia, followed by a reperfusion injury. Recent research indicates that this paradigm is overly simplistic. Development of AKI in sepsis is multifactorial and related to alterations in renal microvasculature blood flow, inflammation, and bioenergetics.

Alterations in Global Renal Blood Flow

Human studies directly quantifying renal blood flow (RBF) in critically ill patients are limited due to the inherent difficulty of safely obtaining measurements in this population. In 2005, Langenberg et al reviewed 162 articles on renal blood flow in sepsis and found that only 3 studies were conducted in humans. The remaining animal studies were confounded by extreme heterogeneity.[14] Roughly two-thirds of the animal-based studies showed a decrease in global RBF, while the remaining studies demonstrated no change or an increase in RBF in septic animals.[14] Multiple factors were examined to account for these divergent findings in the animal studies including method of glomerular filtration rate (GFR) measurement, animal size, sepsis model, cardiac output, techniques and timing of resuscitation and anesthetic use. None of these variables were associated with an increase or decrease in global renal blood flow. After multivariate regression, cardiac output was the only variable associated with global renal blood flow changes, with low cardiac output resulting in low renal blood flow.[14] The authors of that review believe that these results make it difficult to make definitive conclusions about the actual changes in global renal blood flow in the septic patient. Confusing the picture further is the inconsistent relationship between RBF and GFR. Brenner et al examined the relationship between RBF and GFR in a 1990 study in which RBF was measured directly via renal vein catheter in seven adults with sepsis. RBF was maintained in all seven, but GFR decreased in 4 of the 7 patients.[15] In another review article from Langenberg et al, 6 studies including a total of 184 human specimens that underwent histopathology examination found less than one-fourth had evidence of acute tubular necrosis which would be most consistent with injury caused by hypoperfusion.[16] The review showed similar rates of acute tubular necrosis in other experimental models of sepsis including primates and rodents.[16] With this combination of data, it becomes evident that alterations in global renal blood flow are likely of limited impact on pediatric septic AKI.

Inflammation, Microvasculature Blood Flow, Bioenergetics

Considering that roughly 20% of total cardiac output travels to the kidneys, the kidneys are undoubtedly exposed to a broad assortment of inflammatory mediators including tumor necrosis factor (TNF), caspase, thromboxane, interleukin species, and reactive nitrogen species. How the kidneys react to these molecules is likely responsible for the development of organ injury. Current research is broad in scope and describes multiple cytokines that impact the development of septic AKI, but a number of articles have been published, which synthesize these divergent areas of study.[17–19] It is important to recognize that these pathways are acting in parallel. Similarly, there are whole body changes induced by the sepsis phenotype as well as kidney specific responses occurring concurrently.

Sepsis is a potent activator of nitric oxide synthesis; however, localized activation of inducible nitric oxide synthase is heterogenous.[17,19] In the kidney this differential expression may result in the irregular pattern of damage seen on histopathology preparations of septic AKI. Moreover, it is thought that as the kidney is bombarded with other inflammatory cytokines of both pathogen and host origin, the alterations in microvascular blood flow may result in some portions of the kidney experiencing prolonged exposure to the inflammatory modulators leading to further damage and cytokine response by the affected cells[18]