Pathophysiology of septic acute kidney injury: What do we really know?

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Septic acute kidney injury accounts for close to 50% of all cases of acute kidney injury in the intensive care unit and, in its various forms, affects between 15% and 20% of intensive care unit patients. However, there is little we really know about its pathophysiology. Although hemodynamic factors might play a role in the loss of glomerular filtration rate, they may not act through the induction of renal ischemia. Septic acute renal failure may, at least in patients with a hyperdynamic circulation, represent a unique form of acute renal failure: hyperemic acute renal failure. Measurements of renal blood flow in septic humans are now needed to resolve this pivotal pathophysiological question. Whatever may happen to renal blood flow during septic acute kidney injury in humans, the evidence available suggests that urinalysis fails to provide useful diagnostic or prognostic information in this setting. In addition, nonhemodynamic mechanisms of cell injury are likely to be at work. These mechanisms are likely due to a combination of immunologic, toxic, and inflammatory factors that may affect the microvasculature and the tubular cells. Among these mechanisms, apoptosis may turn out to be important. It is possible that, as evidence accumulates, the paradigms currently used to explain acute renal failure in sepsis will shift from ischemia and vasoconstriction to hyperemia and vasodilation and from acute tubular necrosis to acute tubular apoptosis or simply tubular cell dysfunction or exfoliation. If this were to happen, our therapeutic approaches would also be profoundly altered. (Crit Care Med 2008; 36[Suppl.]:S198–S203)

KEY WORDS: sepsis; septic shock; acute renal failure; acute kidney injury; renal blood flow; renal vascular resistance; mean arterial pressure; apoptosis; glomerular filtration rate; cardiac output; cytokines

Acute renal failure (ARF) affects approximately 35% of intensive care unit (ICU) patients (1). Sepsis and septic shock remain the most important cause of ARF in critically ill patients and account for >50% of cases of ARF in the ICU (2).

Despite our increasing ability to support vital organs and resuscitate patients, the incidence and mortality of septic ARF remain high (2). A possible explanation of why mortality has remained high might relate to our limited understanding of septic ARF and its pathogenesis. It is therefore very important for critical care physicians to have an appreciation of what is known and not known about this condition to implement rational therapies. In this article, we review what is known about the pathophysiology of this condition, present the limitations and strengths of the evidence behind our knowledge, and discuss areas that require further investigation.

Definition

Before discussing any condition, it is imperative that there should be a common understanding of the topic. To do this, consensus definitions are needed. Until recently, there was no agreed way to define, identify, and classify septic acute kidney injury (AKI). However, more recently, the Acute Dialysis Quality Initiative developed a consensus definition of AKI that goes under the acronym of *RIFLE* (3). This definition and classification system is described in detail elsewhere in this issue of *Critical Care Medicine*. Its relevance here lies in the fact that together with the widely established consensus definition for sepsis (4), severe sepsis, and septic shock, which has been in use for >15 yrs, it provides a standardized ability to define the presence of septic AKI. Thus, septic AKI is defined by the simultaneous presence both of the RIFLE criteria for AKI and the consensus criteria for sepsis and by the absence of other clear and established, non–sepsis-related (e.g., radiocontrast, other nephrotoxins) causes of AKI. In this regard, a recent study of 41,972 admissions (1) shows that AKI occurs in 35.8% of patients when the RIFLE criteria are applied. A further study of AKI in 54 hospitals from 23 countries shows that close to 50% of AKI is secondary to sepsis (2). Thus, septic AKI probably occurs in somewhere between 15% and 20% of all ICU admissions. Its mortality varies with the severity of AKI from 20.9% to 56.8% (1). The obvious conclusion is that septic AKI is a major problem in ICU patients that requires investigation and a clearer understanding of its pathogenesis.

Pathogenesis

Our understanding of the pathogenesis of human AKI in general and septic AKI in particular is markedly affected by the lack of histopathologic information. This lack of information stems from the risks associated with renal biopsy (especially repeated renal biopsy), which make

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it ethically unjustifiable to obtain tissue from patients who do not have suspected parenchymal disorders such as vasculitis or primary glomerulonephritis. In the absence of such information, we rely on indirect assessments of what might be happening to the kidney. Such assessments are based on blood tests and urine tests and force us to "guess" what might be happening to kidney cells by using indirect forms of assessment, such urine output, urinary sodium concentration, fractional excretion of sodium, fractional excretion of urea, and the like. It is not surprising, therefore, that our understanding of septic human ARF has advanced very little in the last 50 yrs.

To overcome such limitations, animal models of AKI have been developed that enable more sophisticated and invasive measurements to be made. Unfortunately, as recently highlighted (5), these animal models have been mostly based on ischemia–reperfusion injury or drug-induced injury. These models *are not relevant to septic AKI*, and information obtained from such models may be misleading when applied by clinicians to interpret what might be happening to a septic patient who is developing AKI in the ICU.

Renal Blood Flow in Septic AKI. A major paradigm that has been derived from observations in animals and humans with hypodynamic shock (hemorrhagic, cardiogenic, or even septic) is that AKI is due to renal ischemia. This construct implies that restoration of adequate renal blood flow (RBF) should therefore be the primary means of renal protection in critically ill patients (septic or not). Whether RBF in septic patients, in the presence of a normal or increased cardiac output, actually decreases significantly, remains stable, or even increases, however, remains unknown. This is because RBF cannot be measured continuously in humans and even its intermittent assessment requires a high level of invasiveness.

In several experimental studies of septic ARF, global RBF declines after induction of sepsis or endotoxemia (6, 7). This may result not only in a reduction in glomerular filtration but also, if hypoperfusion is severe and prolonged, in metabolic deterioration and diminished contents of high-energy phosphates, possibly causing cell death, acute tubular necrosis, and severe AKI.

On the other hand, other studies show that the renal circulation participates in the systemic vasodilation observed during severe sepsis/septic shock, so RBF does not diminish, and the development of septic ARF occurs not in the setting of renal hypoperfusion but in the setting of adequate and even increased renal perfusion. Ravikant and Lucas (8), for example, studied a pig model of sepsis and showed that during hyperdynamic sepsis, there was an *increase* in global RBF and an increase in medullary blood flow. Brenner et al. (9) developed and studied a percutaneously placed thermodilution RBF catheter in eight critically ill patients with AKI. They demonstrated that sepsis-induced AKI occurred despite normal values of total RBF (10). During human sepsis, patients in the ICU typically show a hyperdynamic circulation. Observations in hyperdynamic models of sepsis may, therefore, be much more relevant to human septic shock. Indeed, the reason why the results of experimental studies are so different in terms of RBF may be entirely related to the animal models (including animal type and type of insult), different methods of measurement, the time and frequency of measurements, and more importantly, the state of the systemic circulation (hypodynamic or hyperdynamic state) (9). In fact, the consistent observation is that once a hyperdynamic state exists, global renal hypoperfusion/ischemia is *not* the norm (11).

A comprehensive review of electronic reference libraries, focusing on experimental models of sepsis and ARF, has been recently published (12). This systematic review found that 160 experimental studies had been conducted that induced sepsis and focused on aspects of renal function or dysfunction and that measured RBF by one of several available techniques. In such studies, close to a third showed that RBF was either preserved or increased in experimental sepsis. To further investigate what factors might influence RBF in experimental sepsis, the authors assessed which experimental variables were associated with preserved or increased RBF. They found that several aspects of the model (awake animal, time from surgery, use of endotoxin, cardiac output) predicted RBF during the experiment. When multivariable logistic regression analysis was used, cardiac output alone remained as the predictor of RBF: high cardiac output sepsis was associated with preserved or increased RBF. Conversely, low cardiac output sepsis (mixed septic and cardiogenic shock) was associated with a low RBF. As noted above, most patients seen in the ICU with sepsis have a high cardiac output state. In recent experimental studies in sheep, in which both cardiac output and RBF were measured continuously and high cardiac output septic state was induced by the infusion of *Escherichia coli*, investigators were able to simulate the typical clinical and hemodynamic state seen in severe sepsis or septic shock (12). Using this model, the investigators were able to show that in hyperdynamic sepsis in a conscious large mammal, RBF is markedly increased and renal vascular resistance in markedly decreased (Fig. 1). In this setting, glomerular filtration rate (GFR) is markedly diminished, with a three-fold increase in serum creatinine concentration and an equivalent decrease in creatinine clearance. In accordance with these findings, renal recovery from this form of septic AKI has been found to be associated with a decrease in cardiac output, an increase in renal vascular resistance, and a decrease in RBF (13). These observations suggest that changes in renal vascular activity (vasodilation) may be important in the loss of glomerular filtration pressure during the first 24–48 hrs of sepsis. They also provide "proof of concept" that glomerular filtration pressure can be lost in septic AKI in the setting of markedly increased RBF. Put another away, septic AKI may represent a unique form of AKI: hyperemic AKI. Such understanding requires a further logical step: an appreciation that GFR is determined by glomerular filtration pressure. Glomerular filtration pressure, in turn, is determined by the relationship between the afferent and efferent arterioles. If the afferent arteriole constricts, glomerular filtration pressure will fall and urine output and GFR will also decrease. However, if the afferent arteriole dilates and the efferent arteriole dilates even more, RBF will markedly increase, yet pressure within the glomerulus will fall. In this setting, GFR will also decrease. This may be the case in human sepsis. To know whether this is indeed the case, one would need to measure RBF in humans during the development of septic AKI.

Unfortunately, little is known about what happens to RBF in humans during severe sepsis or septic shock. This is because measurement of RBF requires invasive approaches. Nonetheless, RBF was measured in a small cohort of patients with sepsis. In these patients, RBF was either preserved or increased (14). To put it

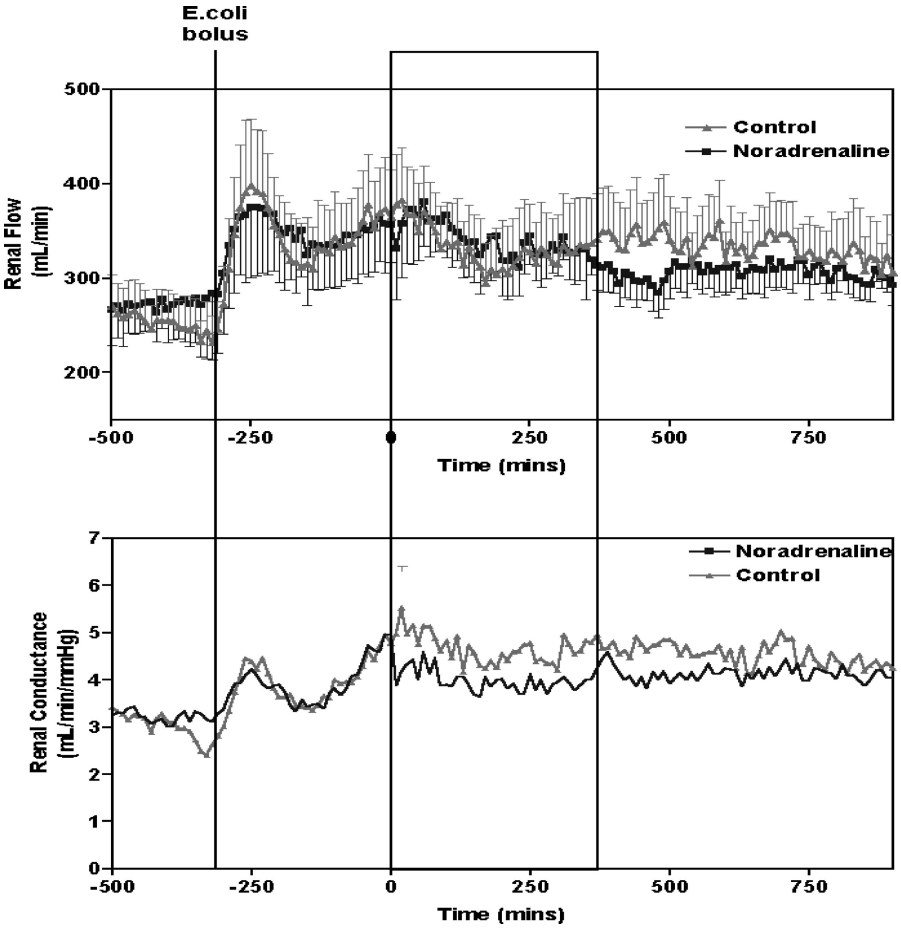

Figure 1. Changes in mean renal blood flow and renal vascular conductance (inverse of resistance) during experimental hyperdynamic hypotensive sepsis in sheep. The timing of *Escherichia coli* (*E. coli*) injection is marked. Renal blood flow and renal vascular conductance in control animals treated with placebo are marked as *triangles*. The timing of noradrenaline (norepinephrine) infusion (*squares*) is framed between 0 and 360 mins. In both groups, there is marked hyperemia and renal vascular vasodilation, which is not altered by noradrenaline infusion (0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

bluntly, we simply do not yet know what happens to RBF in human septic AKI. As this is a crucial issue for our understanding of the pathogenesis of septic AKI, this issue must be the focus of future investigations of the pathogenesis of septic ARF.

In conclusion, renal hypoperfusion might be important in septic AKI associated with hypodynamic states (a relatively uncommon finding in the ICU) but may not play a key role in the development of AKI during hyperdynamic sepsis (the state seen in the vast majority of critically ill, septic patients with severe ARF). Further work is needed in humans to better understand the changes in RBF that occur during septic AKI.

Intrarenal Hemodynamics and Bioenergetics in Septic AKI. It is possible that although there is preserved or increased global RBF in hyperdynamic sepsis, internal redistribution of blood flow favoring the cortex may occur. Unfortunately, no studies have looked at medullary and cortical blood flow in hyperdynamic sepsis with technology that allows continued measurement over time. A recent investigation by our group used laser Doppler flowmetry to continuously monitor medullary and cortical flow in hyperdynamic septic sheep (15). We found that both flows remain unchanged and that the administration of vasopressor (vasoconstrictor) therapy in the form of norepinephrine induced a significant increase in such flows. These observations challenge the view that the medulla is ischemic during hyperdynamic sepsis and simultaneously highlight that hemodynamic factors are indeed at work, which can be modified by interventions capable of affecting systemic blood pressure and cardiac output. In additional work applying a magnetic resonance spectroscopy technique with simultaneous measurement of RBF, we were also able to show that adenosine triphosphate is preserved during septic shock in the sheep (Fig. 2), further supporting the notion that ischemia or bioenergetic failure may not be the primary cause of loss of GFR in sepsis (16, 17). Thus, intrarenal hemodynamic events do occur, which might affect function. However, their favorable modification by vasoconstrictor therapy challenges the widely held view of what is optimal renal resuscitation in septic AKI. Furthermore, although hemodynamic changes might be important, they are likely to represent only part of the mechanisms responsible for loss of function. Other mechanisms may be at work.

Urine Changes in Septic ARF

A variety of textbooks suggest that it is possible to use urinary tests to distinguish acute tubular necrosis (structural injury) from so-called *prerenal ARF* (functional injury). Can this be done in septic ARF? What is the evidence? Recently, we completed a systematic review of the urinary findings seen in experimental models of sepsis and assessed their diagnostic and prognostic value. We found that all tests that are widely promoted as useful did not have sufficient data to support diagnostic accuracy, prognostic value, or clinical utility (18). Similarly, in a systematic review of the value of such tests in humans, we found significant lack of data and a wide variety of findings in septic ARF (19). All of these observations strongly support the concept that, in septic ARF, biochemical analysis of urine using standard measurements of sodium, urea, and creatinine and calculating various indices of tubular function is not diagnostically accurate, prognostically valuable, or clinically useful. More research is needed in this field to better understand the role of urinalysis in sepsis. In this regard, emerging biomarkers of kidney injury may prove more valuable (20).

Nonhemodynamic Injury. From the above discussion, we know that neither global renal hemodynamic changes nor intrarenal hemodynamic changes can be consistently shown to be the sole contributor to septic AKI. There must, therefore, be other mechanisms at work that are not hemodynamic in nature. These factors that contribute to AKI in sepsis might be immunologic or toxic in nature.

Sepsis is characterized by the release of a vast array of inflammatory cytokines,

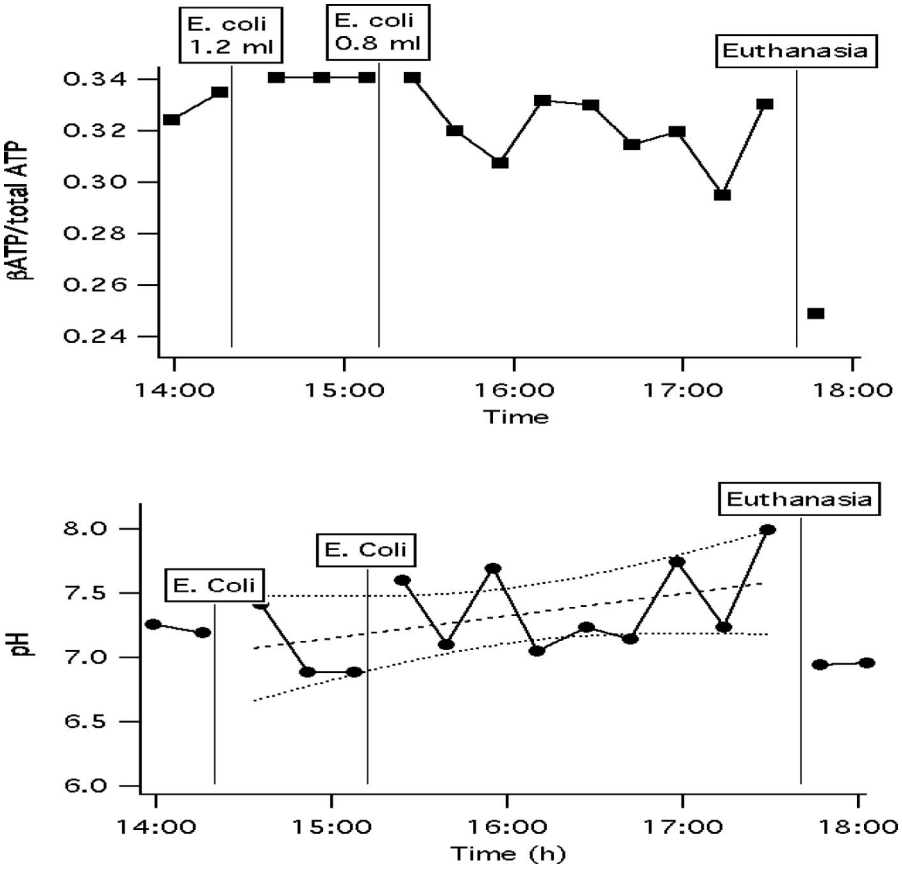

Figure 2. Changes in renal bioenergetics and pH in a model of hyperdynamic hypotensive sepsis in sheep. The timing of *Escherichia coli* (*E. coli*) injection is marked. There is no significant change in β-adenosine triphosphate (*ATP*)/total ATP ratio during sepsis. However, once the circulation stops after the animals are killed, the value plummets to near zero. There is also no evidence of intracellular acidosis until the circulation is stopped.

arachidonate metabolites, vasoactive substances, thrombogenic agents, and other biologically active mediators. A large body of experimental data suggests that these various mediators and neuroendocrine mechanisms might be involved in the pathogenesis of organ dysfunction in sepsis (21).

For example, tumor necrosis factor-α (TNF) has been demonstrated to play a major role in the pathogenesis of Gram-negative septic shock, mediating a broad spectrum of host responses to endotoxemia. In the kidney, endotoxin stimulates release of TNF from glomerular mesangial cells (22). More recently, the direct toxic role of TNF to the kidney has been become clear. Knotek et al. (23), using TNFsRp55-based neutralization of TNF, achieved protection against lipopolysaccharide (LPS)-induced renal failure in wild-type mice. With pretreatment using TNFsRp55, GFR decreased only by 30%, as compared with a 75% decrease without TNF neutralization, suggesting that TNF plays an important role in septic ARF. Cunningham et al. (24) used an intraperitoneal injection of *E. coli* LPS to establish a mice model of sepsis and showed that LPS-induced ARF can be attributed to TNF acting directly on its receptor, TNFR1, in the kidney. Mice deficient in TNF receptor were resistant to LPS-induced renal failure, had less tubular apoptosis, and fewer infiltrating neutrophils. Whereas TNF-receptor–positive kidneys transplanted in TNF-receptor–negative mice developed LPS-induced renal failure, TNF-receptor–negative kidney implanted in TNF-positive mice did not. Thus, TNF seems to be an important direct mediator of endotoxin's effects during septic AKI. These observations suggest that toxic/immunologic mechanisms are important in mediating renal injury during sepsis and that hemodynamic factors do not operate in isolation and may not even be of major importance.

Is Septic AKI Caused by Renal Cell Apoptosis? Apoptosis is a form of cell death that is mediated by a genetically determined biochemical pathway and characterized morphologically by cell shrinkage, plasma membrane blebbing, chromatin condensation, and nuclear fragmentation (25–29). Cells can die by one of two pathways: necrosis or apoptosis. Necrosis results from severe adenosine triphosphate depletion. Such depletion leads to rapid uncoordinated collapse of cellular homeostasis. Apoptosis is an energy-requiring and genetically directed process.

There is now good evidence to show that human renal tubular cells die by apoptosis and necrosis in experimental models of acute ischemic and toxic renal injury (26–29). The endothelial cells can undergo apoptosis in response to a variety of stimuli, especially immune-mediated cell injury via TNF and Fas ligand.

Schumer et al. (29) demonstrated that after a very brief period of ischemia (5 mins), apoptosis bodies could be found at 24 and 48 hrs after reperfusion, without any evidence of necrosis. After more prolonged periods of ischemia, areas of necrosis became evident, but substantial numbers of apoptotic bodies were still seen after 24–48 hrs of reflow. The evidence of whether apoptosis plays an important role in tubular injury *in vivo* remains controversial. It is particularly controversial whether renal cell apoptosis occurs during septic AKI. However, Jo et al. (30) have recently shown that apoptosis of tubular cells by inflammatory cytokines and LPS is a possible mechanism of renal dysfunction in endotoxemia. They found that if high-dose TNF was added to cultured kidney proximal tubular cells, there was increased expression of Fas messenger RNA, the Fas-associated death domain protein, and increased DNA fragmentation. Messmer et al. (31) have also shown that TNF and LPS elicit apoptotic cell death of cultured bovine glomerular endothelial cells that is time and concentration dependent. Their effect was characterized by an increase in pro-apoptotic proteins and a decrease in anti-apoptotic proteins such as Bcl-xL. Unfortunately, TNF blockade with monoclonal antibodies fails to protect animal or kidney during endotoxemia (32, 33). Observations in a preliminary experiment in septic sheep by our group also show that after only 3 hrs of sepsis induced by intravenous injection of *E. coli*, there was expression of early phase pro-apoptotic proteins such as BAX and of counterbalancing anti-apoptotic proteins such as Bcl-xL in the tubular cells, indicating that there is early activation of the apoptotic cascade in septic kidneys.

Organ Cross-talk and Septic AKI. Ventilation of patients with the acute respiratory distress syndrome by means of a low-tidal volume strategy has been shown to reduce mortality (34). The mechanisms for such reduced mortality, however, remain unknown. It is possible that protective ventilatory strategies might affect the well-being of other organs. In a fascinating series of studies, Imai et al. (35) demonstrated that low tidal volume ventilation might protect the kidney from injury in the setting of experimental and clinical acute respiratory distress syndrome. Using a rabbit model of acute respiratory distress syndrome, these investigators found that animals randomized to an injurious ventilatory strategy had increased epithelial cell apoptosis in the kidney and the small intestine. Furthermore, such animals had evidence of renal dysfunction. When renal cells were incubated *in vitro* with plasma from rabbits exposed to an injurious ventilatory strategy, apoptosis of such cells was induced and was markedly greater than seen with exposure to control plasma. These investigators hypothesized that Fas ligand might be responsible for these changes and used FasIg (a fusion protein that blocks soluble Fas ligand) to test this hypothesis. They found that Fas-ligand blockade attenuated *in vitro* apoptosis of renal cells. To further confirm such association, they obtained plasma from patients enrolled in a previous acute respiratory distress syndrome study comparing low-tidal volume ventilation with traditional tidal volume ventilation and found that there was a significant correlation between Fas-ligand levels in plasma and serum creatinine. Given that the vast majority of patients with acute respiratory distress syndrome have sepsis, these observations are highly relevant to septic AKI and highlight yet another pathway potentially responsible for AKI in the setting of sepsis.

CONCLUSIONS

Our understanding of the pathogenesis of septic AKI is limited. Although hemodynamic factors might play a role in the loss of GFR during sepsis, they may not act through the induction of renal ischemia. Septic ARF may represent a unique form of ARF: hyperemic ARF. Measurements in humans are now needed to resolve this pivotal pathophysiological question. Whatever may happen to RBF during septic AKI in humans, the evidence available suggests that urinalysis fails to provide useful diagnostic or prognostic information in this setting. In addition, nonhemodynamic mechanisms of cell injury are likely to be at work, which are immunologic/toxic/inflammatory in nature and may affect the vasculature and the tubular cells. Among these mechanisms, apoptosis may turn out to be important. It is possible that, as evidence accumulates, the paradigms currently used to explain ARF in sepsis will shift from ischemia and vasoconstriction to hyperemia and vasodilation and from acute tubular necrosis to either acute tubular apoptosis or simply tubular cell dysfunction. If this were to happen, our therapeutic approaches would also be profoundly altered. The journey of understanding the pathophysiology of septic AKI has barely started and is likely to be long indeed.

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