# Sepsis-induced acute kidney injury

*Hernando Gómez*[a,b] *and John A. Kellum*[a,b]

**Purpose of review**
Sepsis is a common and frequently fatal condition in which mortality has been consistently linked to increasing organ dysfunction. For example, acute kidney injury (AKI) occurs in 40–50% of septic patients and increases mortality six to eight-fold. However, the mechanisms by which sepsis causes organ dysfunction are not well understood and hence current therapy remains reactive and nonspecific.

**Recent findings**
Recent studies have challenged the previous notion that organ dysfunction is solely secondary to hypoperfusion, by showing, for example, that AKI occurs in the setting of normal or increased renal blood flow; and that it is characterized not by acute tubular necrosis or apoptosis, but rather by heterogeneous areas of colocalized sluggish peritubular blood flow and tubular epithelial cell oxidative stress. Evidence has also shown that microvascular dysfunction, inflammation, and the metabolic response to inflammatory injury are fundamental pathophysiologic mechanisms that may explain the development of sepsis-induced AKI.

**Summary**
The implications of these findings are significant because in the context of decades of negative clinical trials in the field, the recognition that other mechanisms are at play opens the possibility to better understand the processes of injury and repair, and provides an invaluable opportunity to design mechanism-targeted therapeutic interventions.

**Keywords**
acute kidney injury, inflammation, microvascular dysfunction, sepsis, tubular epithelial cells

## INTRODUCTION

Sepsis is the most common cause of acute kidney injury (AKI) in critically ill patients [1▪▪], and sepsis plays a role in 40–50% of cases [2]. Importantly, the development of AKI in the setting of sepsis increases the risk of in-hospital death six to eight-fold [2,3], and among survivors, the risk of progression to chronic kidney disease [4]. Despite this, the mechanisms by which sepsis causes AKI are incompletely understood, and hence current therapy remains reactive and nonspecific. An increasing body of evidence suggests that at least in a proportion of patients, AKI can occur in the absence of overt signs of hypoperfusion, thus suggesting that other mechanisms may be at play. Langenberg *et al.* [5] showed that AKI developed in septic animals despite normal or increased renal blood flow (RBF). Prowle *et al.* [6] demonstrated that decreased RBF was not a universal finding even in patients with well established sepsis-induced AKI, and Murugan *et al.* [7] found that a quarter of patients with nonsevere pneumonia, who were never admitted to an ICU and never had hypotension, still developed AKI.

Recent studies in septic animals and postmortem observations in septic humans have demonstrated that sepsis-induced AKI is characterized by a strikingly bland histology with focal areas of tubular injury, but minimal cell death [8,9], suggesting that acute tubular necrosis (ATN) does not explain this phenotype. A consistent observation regardless of species, disease stage, severity, or organ examined, appears to be the presence of three distinct alterations: diffuse microcirculatory flow abnormalities [10], inflammation [11,12], and cellular bioenergetic responses to injury [9,13]. The study and understanding of these three domains may provide a roadmap to unravel the mechanisms by which sepsis causes AKI and perhaps organ

[a]Center for Critical Care Nephrology and [b]Department of Critical Care Medicine, The CRISMA Center, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to Hernando Gómez, Scaife Hall, 640A, 3550 Terrace Street, Pittsburgh, PA 15261, USA. Tel: +1 412 641 8412; fax: +1 412 641 2645; e-mail: gomezh@upmc.edu

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## KEY POINTS

- Sepsis is the most common cause of AKI, and represents a major health burden because it increases morbidity significantly, predisposes to chronic kidney disease, and increases mortality six to eight-fold.
- Sepsis-induced AKI cannot be fully explained by hypoperfusion and it is not equivalent to ATN, and thus generic treatment such as antibiotics and macrohemodynamic resuscitation are only partially effective.
- Microvascular dysfunction, inflammation, and the TEC response to injury framed by metabolic reprograming are important interacting mechanisms that help explain the clinical phenotype of sepsis-induced AKI.
- The exploration of these mechanisms may yield vital information to understand how sepsis induces organ dysfunction, and thus, to design mechanism-targeted therapeutic strategies.

injury in general and may facilitate the development of more targeted therapies. This review aims to provide the reader with a discussion of the evidence behind these mechanisms, and a proposal for the integration of such mechanisms in the framework of the clinical phenotype of sepsis-induced AKI.

## NOVEL CONCEPTS IN THE PATHOPHYSIOLOGY OF SEPSIS-INDUCED ACUTE KIDNEY INJURY

Recent evidence suggests that the origin of most cases of AKI is multifaceted and that several, concurrent mechanisms may be at play. These mechanisms include inflammation, profound, heterogeneous distortion of peritubular and glomerular microvascular flow, and the tubular epithelial cell (TEC) metabolic response to injury. Given that cell death fails to fully explain the profound functional alterations (because apoptosis or necrosis occur in less than 5% of all TECs), early sepsis-induced AKI may be the clinical and biochemical manifestation of the survival response strategy tubular cells trigger in this context. Evidence from animal studies suggests that such response may be adaptive, and that metabolic reprogramming is crucial to engage the machinery that will not only safeguard the cell from energy imbalance by downregulating energy consumption but also will determine the characteristics of the response and the repair phenotype once inflammation has abated.

### The renal microcirculation during sepsis-induced acute kidney injury

Sepsis causes profound alterations in microvascular blood flow [10,14] characterized by an increase in the heterogeneity of regional blood flow distribution and an increase in capillaries with deficient blood flow (i.e., intermittent or stopped flow) [10,15]. The renal microcirculation is disturbed in a similar fashion during sepsis-induced AKI [12,16,17], even with normal or increased global organ RBF [18]. Multiple mechanisms seem to frame this characteristic microcirculatory derangement, including endothelial dysfunction, impaired red blood cell deformability, damage and shedding of the glycocalyx layer, increased leukocyte activation, adhesion and recruitment, platelet adhesion, and activation of the coagulation cascade with fibrin deposition [15,19] (Fig. 1).

Importantly, these alterations in microcirculatory flow and endothelial function are thought to contribute directly to the development of organ dysfunction through multiple mechanisms. Retrograde endothelial communication, central to maintain coupling of microvascular flow to tissue metabolic demand (i.e., autoregulation) and to regulate vascular tone is lost during sepsis [20,21], suggesting an increase in the risk of shunting and development of areas of hypoperfusion [22,23]. Endothelial dysfunction is associated with altered barrier function, with consequent increased vascular permeability and worsening interstitial edema [24,25]. In this context, edema represents a risk for local oxygen delivery because it may increase the diffusion distance of oxygen from the capillary to the corresponding target tissue [26], and because it increases venous output pressures (this is especially important in the kidney as it is an encapsulated organ) [27–29].

Nitric oxide has also been shown to play an important role in the pathophysiology of AKI, as its nonselective inhibition can restore microvascular flow and preserve renal function [16]. As described previously [30▪], despite overall increased nitric oxide production during sepsis [31], the heterogeneity of expression of inducible nitric oxide synthase [31] results in the creation of areas devoid of nitric oxide and vasodilatatory capacity, and thus at risk of shunting and hypoxia [32]. Sepsis also results in an inducible nitric oxide synthase-dependent decrease in endothelial-derived nitric oxide synthase activity, which also alters microvascular flow homeostasis [33,34]. Along with inflammation and oxidative stress, uncoupling of endothelial-derived nitric oxide synthase [35] results in loss of regulatory and defense mechanisms like direct

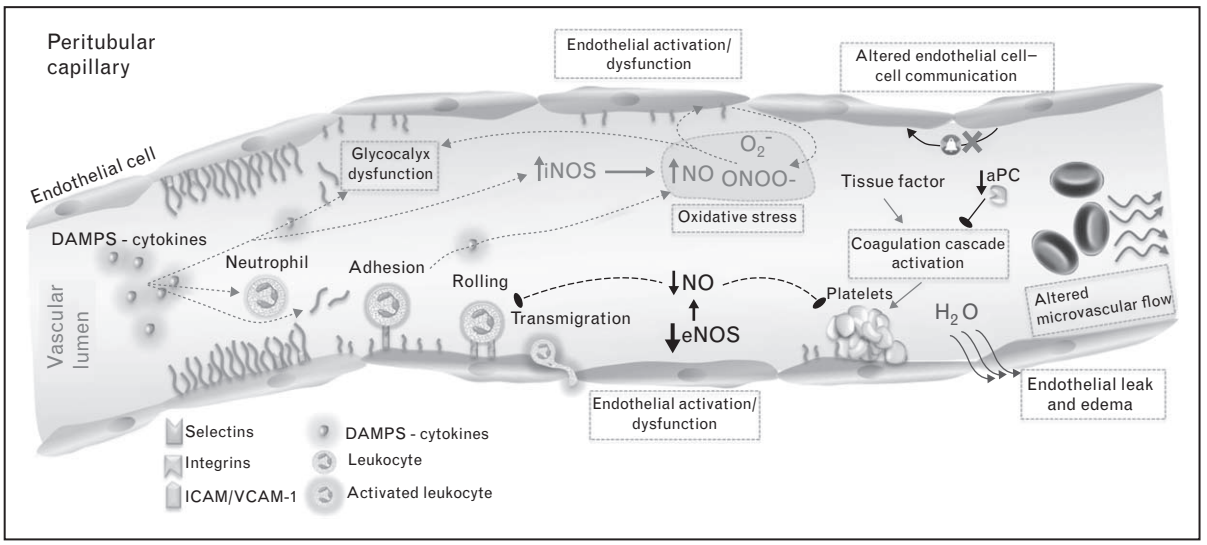


**FIGURE 1.** The figure summarizes the mechanisms that are thought to participate in the development of microvascular dysfunction. Damage-associated molecular patterns and pathogen-associated molecular patterns resulting from invading pathogens and the subsequent immune response activate leukocytes and endothelial cells. Activation of, and injury to endothelial cells directly or through oxidative stress, induces alterations in protective mechanisms (see text). In addition, damaged or activated endothelial cells undergo shedding of their glycocalyx which exposes adhesion molecules to circulating leukocytes and platelets, promoting adhesion of both, and rolling and transmigration of leukocytes; alters the barrier function of the capillary, resulting in capillary leak and formation of edema; alters sensing of shear stress forces which are necessary to regulate tone and couple blood flow to changing circumstances; and causes profound alterations in blood flow distribution. DAMPs, damage-associated molecular patterns; eNOS, endothelial-derived nitric oxide synthase; iNOS, inducible nitric oxide synthase; NO, nitric oxide. Adapted with permission from [19].

vasodilatation, inhibition of platelet, and leukocyte aggregation and preservation of the glycocalyx. The glycocalyx is a layer of organized glycosaminoglycan branches that protrudes from the surface of the endothelial cell membrane into the capillary lumen, which fulfills important biomechanical functions [36]. Damage and loss of the glycocalyx layer is thought to result in altered red blood cell flow, capillary leak, and exposure of endothelial adhesion molecules, which leads to increased adhesion of platelets and leukocytes.

Sluggish peritubular flow may also result in amplification of the inflammatory signal because prolonged transit of activated leukocytes may translate into a greater time of exposure of neighboring endothelial and epithelial cells to damage and pathogen-associated molecular patterns [37] (Fig. 2).

As part of the specialized renal microcirculatory network, glomerular dynamics are also altered during sepsis, resulting in the characteristic decline in glomerular filtration rate (GFR) in the setting of sustained RBF. It is important to preface the discussion on intraglomerular alterations that will follow, by noting the effects of blood flow distribution in the setting of microvascular dysfunction during sepsis. Increased heterogeneity of blood flow results in heterogeneous distribution with some nephrons receiving low flow, whereas other nephrons receive hyperemic flow, while recruitment of alternative pathways (i.e., like Ludwig's artery from efferent to afferent arterioles) [39,40] can bypass (shunt) the glomerulus altogether. This explains at least in part how GFR can drop (as a result of the effect of the sum of nephrons with low flow and shunted blood through alternative pathways) while global RBF into the kidney is maintained. The decline in GFR is further explained by the intraglomerular alterations characteristic of sepsis. Because GFR depends on the generation of sufficient net filtration pressure within the glomerular capillary, and net filtration pressure depends on the balance of forces favoring (glomerular capillary hydrostatic pressure – $P_C$, and glomerular capillary oncotic pressure – $\pi_C$) and opposing (hydrostatic pressure in Bowman's space – $P_B$,) the exit of fluid into Bowman's capsule, the drop in GFR during sepsis can only be explained by three possible events: a decline in mean arterial pressure (which drives glomerular capillary hydrostatic pressure), vasoconstriction of the afferent arteriole, and predominant vasodilatation of the efferent arteriole [40]. Vasodilatation of the efferent arteriole has been shown to occur during sepsis, and has been postulated to be potentially protective because a decline in GFR will result in less exposure

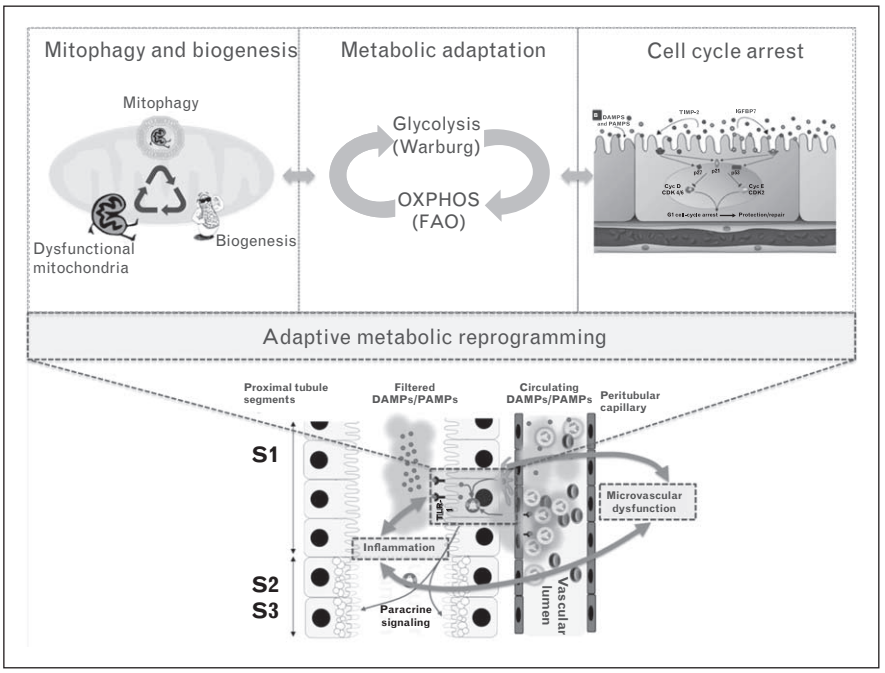


**FIGURE 2.** The figure represents a potential model to explain how the interactions between sepsis-induced microvascular dysfunction, inflammation and the metabolic response from TECs interact. It is still unknown if these are the only interactions, if the directions of the interactions are correct, and what is the sequence of events that spins this injury-response cycle into reverberation. Here, the response of the TEC to injury is governed by metabolic reprogramming. Through this, the TEC is able to optimize energy production and prioritize energy expenditure, while supporting the necessary supply of carbon, nitrogen and other components for the synthesis of proteins and structural components necessary to mount an innate immune response. This may be achieved early on by activating a series of master regulators of cellular metabolism that ultimately are capable of switching between aerobic glycolysis and OXPHOS, and engaging other processes necessary for the survival of the cell such as autophagy (mitophagy) and biogenesis. In addition, cell cycle arrest may be a complementary important protective strategy to avoid the overtaxing energy expenditure and the risk of replicating damaged DNA during mitosis, particularly in the context of scarce energy resources. AKI, acute kidney injury; DAMPs, damage-associated molecular patterns; OXPHOS, oxidative phosphorylation; TEC, tubular epithelial cell. Bottom panel is adapted with permission from [37], and cell cycle panel is adapted with permission from [38▪].

to filtered damage and pathogen-associated molecular patterns and in decreased energy utilization because less ion reabsorption is needed with less tubular flow. Indeed, sepsis-induced tubular injury has been associated with a decrease in tubular reabsorption of sodium [41]. Furthermore, increased delivery of NaCl to the macula densa triggers the vasoconstriction of the afferent arteriole by a mechanism known as tubuloglomerular feedback [42], thus decreasing GFR further.

## The (adaptive) responses of tubular epithelial cells to inflammation

Despite multiple triggers for apoptosis occurring during sepsis, significant necrosis and apoptosis do not occur in the kidney during sepsis [8,9,43]. This finding suggests that during the acute phase, regardless of the consequences at the organ level, the cellular response is successful at preventing death. This denotes a likely underlying adaptive mechanism [9,37,44]. In addition, the recognition that TECs are actually equipped with machinery to recognize the inflammatory signal, including Toll-like receptors (TLRs; i.e., TLR2 and 4), supports the hypothesis that their response may be part of a well coordinated effort to maintain cellular integrity even at the risk of short-term organ dysfunction [37]. Accordingly, it is reasonable to think that the TEC response to injury may be characterized at least in part by processes that limit pro-apoptotic triggers, by reprogramming metabolism to optimize and prioritize energy consumption, and maintain energy homeostasis; maintaining of cellular organelle function through quality control processes (general autophagy and mitophagy); and limiting cell cycling and DNA replication (high-energy requiring processes).

## Metabolic reprogramming and reprioritization of energy consumption

Analogous to the evolutionarily conserved defense response to hypoxia, where nonvital functions are limited to avoid overtaxing energy expenditure [45], administration of lipopolysaccharide (LPS) has been shown to downregulate renal TECs ion transporters [46], which account for more than 70% of ATP consumption [47]. Good *et al.* [48] have shown in an LPS-induced rodent sepsis model that LPS inhibits NHE1 ($Na^+/H^+$ exchanger 1), and Hsiao *et al.* [41] have shown that sodium transport (tubular sodium reabsorption) is decreased as early as 9 h after induction of sepsis by cecal ligation and puncture (CLP). These data suggest that inflammation is associated with downregulation of ion transport although the mechanisms leading to this are still incompletely understood.

Prioritization of energy expenditure during sepsis seems to be part of a more complex cellular metabolic reprogramming strategy, which is key to the survival of the cell in the acute phases of the septic syndrome, and may determine the repair phenotype during the convalescent phase. A phasic switch between glycolysis and oxidative phosphorylation (OXPHOS), similar to that seen in cancer cells (i.e., Warburg effect) [49] has been shown to frame the biochemical phenotype of this metabolic reprogramming in immune cells during early sepsis. Yang *et al.* [50] demonstrated that knockdown or inhibition of pyruvate kinase isoenzyme 2, an enzyme required for the Warburg effect to occur in monocytes during inflammation, improved the survival of septic rodents. Although the evidence is significantly less robust in TEC, Waltz *et al.* [51] using metabolomics analysis have shown data supporting a potential shift from OXPHOS to aerobic glycolysis in renal tissue during the acute phases of murine CLP-induced sepsis. Furthermore, the activation of master regulators of energy balance that promote OXPHOS over glycolysis before or after the induction of sepsis by CLP, protects from AKI in rodent models [52▪,53▪] suggesting that metabolic reprogramming may also be important in the response of the TECs.

Early and phasic metabolic reprogramming has also been shown to be a determinant of the repair phenotype during convalescent phases in surviving animals, and potentially humans. Han *et al.* [54▪] have demonstrated that restoring deficient fatty acid oxidation (FAO) in animals lacking the liver kinase B1, an upstream FAO and AMPK regulator using fenofibrate [a peroxisome proliferator-activated receptor (PPAR) α and the PPAR-γ coactivator-1a agonist, which is a key promoter of FAO], rescued animals from renal tissue fibrosis. In agreement with these findings, Kang *et al.* [55▪▪] have shown a decreased tissue expression of FAO promoters and enzymes in animals and humans undergoing renal fibrosis, and have recapitulated this phenotype by deliberately inhibiting FAO metabolism.

Taken together this evidence suggests that during sepsis, the response of the TEC may be characterized by an organized reprogramming of metabolism, that promotes hierarchical down-regulation of major energy sinks like ion transport, whereas only fueling processes necessary to cell survival (i.e., maintenance of membrane potential) [56], and that adjusts energy and substrate acquisition between glycolysis and OXPHOS to adapt to changing environmental conditions (Fig. 2). This evidence also suggests that reprogramming of metabolism as a defense strategy goes beyond the acute phases of the septic syndrome, defining the repair phenotype, and thus influencing the risk of progression to chronic organ dysfunction.

## Mitochondrial quality control processes: mitophagy and biogenesis

Mitochondria are common targets of inflammatory injury, which leads to dysfunction, increased production of reactive oxygen species (ROS) and thus harm to the host cell. However, the cell can defend from injured mitochondria by triggering quality control processes that attempt to repair dysfunctional mitochondria (fusion and fission), digest and eliminate those beyond the possibility of repair (a specialized form of autophagy called mitophagy) [57,58], and reconstitute the pool of healthy mitochondria (biogenesis). Importantly, mitochondrial function and quality control processes are intimately linked to the metabolic changes triggered by inflammation during sepsis because OXPHOS occurs within mitochondria and depends on a functional mitochondrial pool, and also because many of the upstream regulators of metabolism directly control mitochondrial dynamics.

During sepsis, TLR-mediated inflammation [59], oxidative stress [60,61], and alterations in the electron transport chain that uncouple respiration are potent triggers of mitophagy and biogenesis [58]. In the kidney, mitophagy is activated in the kidney as early as 3 h after CLP-induced sepsis [41]. Importantly, insufficient activation of mitophagy has been associated with worse outcome in critically ill patients, and it has been postulated to contribute to cell and organ dysfunction [62]. Stimulation of mitophagy has been shown to be effective at protecting cells [41] and organ function [62] in the

setting of sepsis [63], whereas decreased autophagy has been associated with increased markers of AKI [41]. In addition to common triggers, recent evidence has suggested that mitophagy and biogenesis are coupled through several mechanisms, including redox pathways and TLR9-dependent mechanisms [64], and that biogenesis also fulfills a role in the defense of the TEC to inflammation. Tran *et al.* [65] demonstrated that animals lacking peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which regulates the activation of biogenesis, were more susceptible to developing AKI after exposure to endotoxin than wild type animals. Activation of mitochondrial biogenesis is a natural response of TECs during sepsis, as demonstrated by Bartz *et al.* [66▪] in a murine model of *Staphylococcus aureus*-infected peritoneal clot. MacGarvey *et al.* [67] further demonstrated that exogenous activation of mitochondrial biogenesis using inhaled carbon monoxide at 250 ppm significantly increased survival, suggesting biogenesis as a potential therapeutic target. As a protective response, mitophagy and biogenesis offer several advantages, namely, removal of dysfunctional mitochondria and thus decreased ROS/reactive nitrogen species production, maintenance, and renewal of the mitochondrial pool with energy conservation, limiting oxidative stress damage, and importantly, intercepting proapoptotic signals at the mitochondrial level impeding triggering of apoptosis [58,68–71].

### Cell cycle arrest

There is a growing body of evidence indicating that mitochondria are intimately involved in the regulation of the cell cycle [58], and that cell cycle arrest may be an important cellular defense strategy in the context of sepsis [37]. Yang *et al.* [72] showed in a rodent model of CLP-induced sepsis that G1-S cell cycle arrest was associated with kidney injury and that recovery of renal function paralleled cell cycle progression 48 h after CLP. Although in the context of metabolic downregulation cell cycle arrest may provide protection in the early stages by limiting the cost of replication and the consequences of duplicating damaged DNA, cell cycle progression and cell replication may be required for adequate repair at later stages and thus, persistence in arrest may prove deleterious. For this reason, clarifying the impact of timing of cell cycle arrest or progression on cell injury and repair is crucial to understand a key mechanism of cell protection, and fundamental to translate this mechanism into targeted therapeutic interventions. Importantly, this mechanism may have direct clinical relevance because recently, the tissue inhibitor of metalloproteinases 2 and insulin-like growth factor-binding protein 7, two markers involved in G1-S cycle arrest, have been identified as the most sensitive and specific markers to predict risk of development of AKI in critically ill patients [73▪,74,75].

## CONCLUSION

The recognition that in the case of the kidney, sepsis-induced AKI cannot be entirely explained by the traditional concept of ATN, and that sepsis does not cause overt apoptosis and necrosis in failing organs, has challenged the notion that ischemia is the only mechanism explaining organ dysfunction. Importantly, it has also prompted many to suggest that the response to the septic environment may, early on, be adaptive in nature. In this review, we have focused on three fundamental mechanisms that may interact in a harm-response cycle (Fig. 2) to explain the pathophysiology of sepsis-induced AKI: microvascular dysfunction, inflammation, and the cellular response to the inflammatory insult. We have described evidence that demonstrates the fundamental role metabolic reprogramming has as a driver of the adaptive response and as a protective mechanism that not only limits cell injury in the acute phase but also that transcends to convalescence by defining the repair phenotype. Further work is warranted to better understand the role, timing and reach of these multiple mechanisms and the relationships between them (i.e., what comes first?) in the pathogenesis of sepsis-induced AKI, and if this can be translated into novel diagnostic and therapeutic interventions to improve outcome in this patient population.

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### Conflicts of interest

*There are no conflicts of interest.*

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