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Understanding acute kidney injury in sepsis

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Acute kidney injury (AKI) affects approximately 40 % of critically ill patients [1] using the latest clinical Kidney Diseases: Improving Global Outcomes (KDIGO) criteria based on both serum creatinine and urine output [2]. The impact of AKI on outcome is substantial. One-third of critically ill patients with AKI die before day 90 [1], and the attributable excess 90-day mortality is approximately 10 %. Septic AKI accounts for approximately half of all AKI cases in the critically ill patients [3]. Yet, the pathophysiology of septic AKI is still inadequately understood. Previous suggestions highlighting systemic hypotension, renal vasoconstriction, and ischemia–reperfusion injury as the major mechanisms for septic AKI have been challenged by reproducible experimental large animal models. Such models show that septic AKI occurs in the setting of renal vasodilatation and increased renal blood flow (RBF) [4]. Thus, pathophysiological mechanisms which differ from the traditional "ischemia paradigm" may instead be responsible for septic AKI. Recently proposed mechanisms for the loss of glomerular filtration rate (GFR) seen in septic AKI comprise dominant efferent arteriole dilatation (compared to afferent arteriole) and subsequent decrease in glomerular filtration pressure ("intraglomerular hypotension"), intra-renal hemodynamic alterations (periglomerular shunting), excessive inflammatory activation, or any combination of the above factors (Fig. 1).

More recently a unified theory for septic AKI combining inflammation, microcirculatory dysfunction, bioenergetics, and tubular cell adaptation to injury has been proposed [5]. The relationship between tubular cell injury and loss of GFR in septic AKI, however, remains poorly understood. The suggested [5] explaining mechanism for this relationship is activation of the tubuloglomerular feedback (TGF) which leads to afferent arteriolar vasoconstriction, decreased hydrostatic pressure in the glomerulus, and a subsequent decrease in GFR. However, it is not clear whether tubular injury contributes to loss of GFR or whether the two processes proceed in parallel and simply represent two sides of the same coin. For example, TGF activation should induce afferent arteriole vasoconstriction, but present experimental and human data suggest the opposite. Furthermore, the preserved normal histology [6] of glomeruli and limited tubular injury in septic AKI is still puzzling in light of the marked functional loss seen clinically. The postmortem histopathological findings in septic AKI have shown little or no acute tubular necrosis [7].

Although progression of septic AKI has been associated with time-adjusted hypotensive load in an

observational multicenter cohort study [8], other studies indicate that AKI may also develop in hyperdynamic septic shock with preserved or even increased RBF [9]. Regrettably RBF cannot be measured continuously in septic humans, and thus, the possible benefit of interventions targeting hemodynamic improvement can only be based on systemic hemodynamic parameters such as mean arterial pressure (MAP) or cardiac output (CO). However, MAP, CO, RBF, and GFR have been unpredictably related in septic patients [10, 11] and in experimental settings. Nevertheless, it seems clinically plausible that in septic shock with increased lactate levels vasopressors may prevent further drop in MAP and subsequent further damage. However, there is a need for further studies before they are considered as therapeutic targets for manipulation.

Growing evidence suggests that the pathophysiology of septic AKI is multifactorial and may differ between patients [4]. In general, immunologic and inflammatory factors seem to be dominant. A recent review [5] summarized the literature supporting a theoretical framework of septic AKI as an adaptive response of the tubular cells to an injurious inflammatory signal. Inflammatory mediators derived from activated immune cells and directly from pathogens, also called damage or pathogen-associated molecular patterns (DAMPs and PAMPs) are recognized by the immune system to fight the infection, but simultaneously cause host cell injury (Fig. 1). Tubular cells can recognize DAMPs and PAMPs by several receptors, including toll-like receptor 4 leading to overexpression of NF-κB and tumor necrosis factor α (TNF-α) by a messenger molecule, myeloid differentiation factor 88. Such activation can cause tubular cell injury. TNF-α has been shown to induce direct renal injury and to be an independent predictor of septic AKI supporting its relevance in the pathogenesis. Experimental data also support programmed cell death, apoptosis, as the potential mechanism of tubular cell death in ischemic and toxic renal injury. The role of apoptosis in septic AKI is still controversial. However, there are supportive data from experiments with cultured renal tubular cells, postmortem studies, and animal experiments.

Other proposed mechanisms behind septic AKI include organ cross-talk linking lung and kidney injury [12] and microvascular dysfunction and heterogeneity in local RBF resulting in areas of hypoperfusion and hypoxia, oxidative stress response, and alterations in cell energy consumption driven by mitochondria [5]. Microcirculatory disturbances including endothelial damage, coagulation disturbances, and glomerular shunting within the kidney may play a significant role [13]. The relative importance of each of these mechanisms in human septic AKI has not been elucidated yet. However, experimental data suggest that ischemia or bioenergetics failure may not be a primary cause of septic AKI, because cortical and

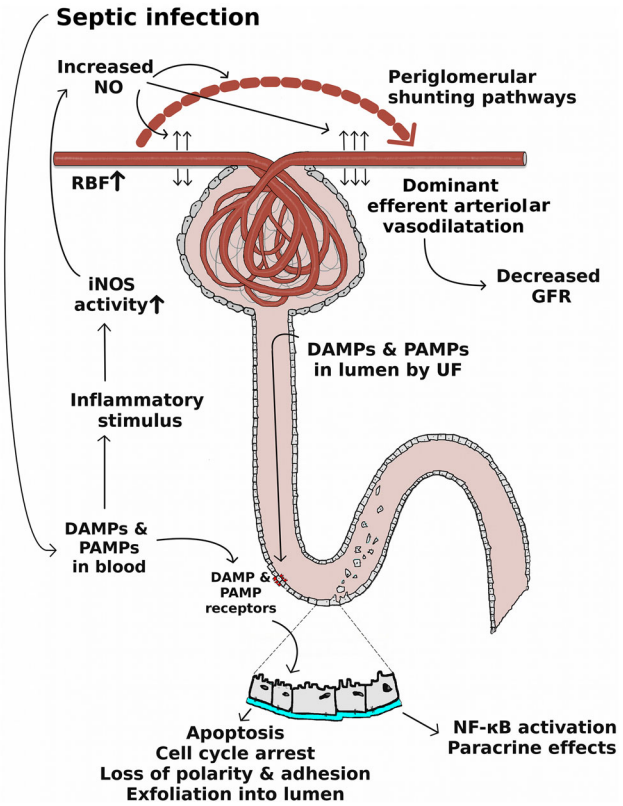

Fig. 1 Simplified illustration of the proposed pathophysiological mechanisms in septic acute kidney injury. *NO* nitric oxide, *RBF* renal blood flow, *iNOS* inducible nitric oxide synthase, *DAMPs* damage-associated molecular patterns, *PAMPs* pathogen-associated molecular patterns, *GFR* glomerular filtration rate, *UF* ultrafiltration

medullary blood flow, renal vascular conductance, and adenosine triphosphate levels [14] remained unchanged in hyperdynamic septic sheep. In addition, RBF, renal mitochondrial respiration, or renal lactate/pyruvate ratio did not change in experimental endotoxemia [15].

In conclusion, despite marked progress in our understanding of the pathophysiology of septic AKI over the last decade and the emergence of new ideas and paradigms, there are still major gaps in our knowledge. It seems plausible that the pathophysiological mechanisms behind septic AKI are multiple and may differ between patients and according to the timing of the septic insult. Further experimental and human data using the latest standard definitions of sepsis and AKI, the greater application of novel biomarker measurements and molecular biology techniques, and the use of novel magnetic resonance technology for the estimation of RBF will likely be applied to increase our understanding of septic AKI in the next decade.

Until we reach a better understanding of why and how septic AKI develops, we will not be able to deploy logical

therapeutic interventions to prevent or treat septic AKI and test them in adequately powered controlled trials.

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Conflicts of interest The authors declare no conflicts of interest.

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