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Review

Pathophysiology of sepsis-associated AKI [SA-AKI]

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ABSTRACT

Sepsis often leads to widespread injury causing multiple organ dysfunction and the development of AKI in sepsis often portends poor prognosis. The pathophysiology of sepsis induced AKI is complex and multifactorial. Initially it was thought that hypotension causing hypoperfusion of kidneys as the major cause of AKI in sepsis. Recent work has been shown that rather than hypoperfusion, microvascular dysfunction with release of inflammatory mediators, cytokines, microparticles with adaptation of tubular cells as the major contributor of sepsis induced AKI. The aim of this review is to focus on the recent advances in pathophysiology of sepsis induced AKI and understanding these complex mechanisms which may pave the way for newer treatments in the future which are directed against the specific pathophysiological mechanisms.

1. Introduction

Sepsis-associated acute kidney injury (SA-AKI) leads to a high burden of morbidity and mortality in patients who are critically ill. The pathophysiology of SA-AKI is not completely known and it represents a subset of AKI characterized by a unique hemodynamic and inflammatory mechanisms. SA-AKI poses significant therapeutic challenges for clinicians, as there has been no specific treatment strategy to alter the natural history of SA-AKI. Rather, current strategies focus on early clinical risk identification, detection of injury, early appropriate antimicrobial therapy, and surveillance for long-term damage among survivors of SA-AKI.

2. Histopathology

Finding the exact histopathologic findings of kidney in septic AKI is not very common as kidney biopsies are not performed for AKI in sepsis routinely. In a systematic review of histopathology of septic AKI in humans, it was found that histopathological features suggestive of acute tubular necrosis were found in around 20% of biopsy samples and the rest of histological specimens were relatively normal looking although the morphologies were highly variable and there were no consistent changes in the renal histopathology in septic AKI.[1]

In the histopathologic findings of experimentally induced septic AKI model by Langenberg et al.,[2] neither significant macrophage infiltration or tubular injury was found nor was there evidence of cell death [apoptosis/necrosis]. It is therefore thought that AKI in septic kidney is rather a functional phenomenon without significant histologic or immunohistologic changes.

The histopathology of AKI in septic kidney is characterized by focal areas of tubular injury with apical vacuolization without significant apoptotic or necrotic changes in the tubules.[3]

3. Pathophysiology

The basic mechanisms in the pathophysiology of AKI in sepsis are complex and not completely clear.[4,5] The pathophysiology of sepsis associated AKI can be explained by the following mechanisms. As the role of each of the following cannot be determined individually, a unified theory has been put forward by Gomez et al.[6] to explain the mechanism of sepsis-associated AKI, in which they have described the interplay between inflammation and oxidative stress, microcirculatory dysfunction, and the response of

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tubular epithelial cell to the septic injury, as are the important mechanisms for AKI in sepsis.

3.1. Macrovascular abnormalities

Most of the common causes of AKI like hypovolemia, sepsis, and major surgery were associated with shock but ischemia cannot be attributed to all causes of AKI. However, AKI can occur in the absence of hypoperfusion, either global or regional. Although in the previous studies renal vasoconstriction, systemic hypotension, and ischemia-reperfusion injury were the main primary pathophysiological mechanisms involved in sepsis-induced AKI, in experimental septic AKI induced in rats, it has been shown that renal vasodilatation and increased renal blood flow occur in sepsis-induced AKI.[1,7]

3.2. Changes in glomerular hemodynamics

Even though the renal blood flow is increased during septic AKI,[7] GFR is not increased, rather it is decreased, and it can be ceased completely also. Predominant dilatation of the efferent arteriole during sepsis causes decrease in hydrostatic pressure in glomerular capillaries and thereby decreases in the net filtration pressure.

A decreased GFR is the major functional event of septic AKI and this acts as a protective mechanism against further insults of sepsis by decreasing filtration of toxins, such as DAMPs [Damage-Associated Molecular Patterns] and PAMPs [Pathogen-Associated Molecular Patterns], and thereby decreasing exposure of tubular cell to DAMPs and PAMPs. Decreased GFR also leads to decreased energy consumption because the filtered load of NaCl is less.

Impaired reabsorption of sodium chloride by the injured tubules leads to increased delivery of NaCl to macula densa, which is sensed by Na-K-2Cl channel leading to turning off of tubuloglomerular feedback (TGF) leading to afferent arteriolar constriction and blunting of sepsis-induced afferent vasodilatation.[8] Additionally, during sepsis, sympathetic nerve activation will further counterbalance afferent vasodilatation and contribute to decreased GFR and oliguria.[9] Systemic vasodilatation leading to shunting of blood from glomerular capillaries (glomerular shunt pathways) leads to the decreasing GFR and thereby decreasing kidneys' exposure to PAMPs, DAMPs, Reactive oxygen species, and Reactive nitrogen species.[10,11]

In patients with sepsis, higher central venous pressure (CVP) was associated with increased risk of developing AKI.[12] In a micropuncture study in rat peritubular capillaries, a 2.6-fold increased risk of AKI was found when CVP increased from 6 to 15 mmHg.[13] Elevated CVP causes increase of renal venous pressure, which was associated with elevated renal interstitial and intratubular pressure.[13] In sepsis, raised central venous pressure (CVP) due to systemic venous congestion accompanied by local renal venous congestion and renal interstitial edema also contribute to the sepsis-induced kidney dysfunction.[14] As the renal capsule surrounding kidney is noncompliant, intrarenal pressure increases exponentially with increase in renal volume[15] leading to reduction in transrenal pressure gradient causing reduced RBF and increased intratubular pressure counteracting net filtration pressure.

3.3. Microvascular abnormalities

Sepsis causes alteration of blood flow in both microvascular, as well as macrovascular beds. Microvascular dysfunction is characterized by a significant decrease in capillary density that occurs wherein there is decrease in the number of capillaries with continuous or nutritive blood flow, along with increase in number of capillaries with intermittent or no flow.

The cortex receives a large amount of blood necessary for the filtration function. In contrast, the flow in vasa recta is sluggish, which is required for maintenance of the corticomedullary gradients. During sepsis, initially it was thought that renal hypoperfusion is the main contributor for renal hypoxia.

Despite equal risk of all nephrons in the kidney being exposed to these mediators, only patches of tubular cells are exposed to these mediators. This noncontinuous involvement of tubule is due to heterogeneous blood flow due to microvascular dysfunction. The sluggish peritubular flow in the peritubular capillaries due to microvascular dysfunction leads to a longer transit time for activated leukocytes, resulting in a longer exposure time of the endothelium to cytokines, PAMPs, and DAMPs, which then triggers more inflammatory signals and increases oxidative stress. The surrounding tubular epithelial cells are also exposed to these inflammatory signals, which lead to increased oxidative stress and adaptation of bioenergetics to the microtubular environment, ultimately signaling other tubular cells to shut down.

The accumulation of inflammatory cells, causing microcirculatory disturbance with hypoxia, tubular obstruction from cellular debris, and back-leak, lead to increase of tubular and interstitial pressures, which leads to decreased pressure gradient across the glomerular capillary and tubular space, thereby decreasing the GFR. In addition, interstitial edema resulting from capillary leakage will further compromise blood flow and hypoxia.

Sepsis-induced AKI occurs as an adaptive response of tubular cell to inflammatory signal associated microvascular dysfunction, endothelial cell injury, which leads to mitochondrial orchestration of complete metabolic shut down with reprioritization of energy towards cell survival at the expense of tubular absorption, and secretion of solutes.

3.4. Activation of coagulation cascade

Engelmann et al.[16] proposed the "theory of immunothrombosis," which suggested that clot formation in small amounts was beneficial for host as the bacteria and DAMPs were trapped and kept away from host circulation. Tissue factor upregulation, loss of function of tissue factor pathway inhibitors, increased destruction of AT resulting in excessive thrombin activation, and decreased production of activated protein C give favor to microthrombi formation and subsequent microvascular injury.

3.5. Role of nitric oxide (NO)

Sepsis causes heterogenous inducible NO synthase (iNOS) production resulting in great variation of regional NO concentrations, leading to depleted NO in some vascular beds despite elevated globally systemic NO levels. In an experimental septic kidney study done by Langenberg et al.,[2] it demonstrated that there is overexpression of all iNOS isoforms in the renal cortex but not in the renal medulla during sepsis, which may induce intrarenal shunting.

3.6. Role of inflammation

During sepsis, PAMPs [Pathogen-Associated Molecular Patterns], the macromolecular motifs [derived from pathogens] and DAMPs [Damage-Associated Molecular Patterns] derived from activated immune cells mediate host cellular injury.

Toll-like receptors (TLRs) are a type of pattern recognition receptors[17,18] located on surface of multiple immune and nonimmune cells and play an important role in host immune response to pathogen by recognizing microbe-derived PAMPs. In "the danger model," proposed by Matzinger[19] the injured or dying host cells send out "danger signals" called DAMPs to activate