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PREVENTING ACUTE KIDNEY INJURY IN SEPSIS

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Abstract:
Acute kidney injury is a common and life-threatening complication of sepsis. It is known to be associated with at least 50% mortality. Therefore, understanding the pathogenesis and prevention of sepsis-induced acute kidney injury has been a subject of concern for may decades. Although the details of the basic mechanisms of the condition remain elusive, some processes were discovered, and many advances were made. Sepsis-induced acute kidney injury occurs due to complex mechanisms that act synergistically to damage renal tissue. The main revealed mechanisms are microcirculatory dysfunction, systemic inflammation, and local maladaptive response of the renal tissue. Prevention of acute kidney injury among patients with sepsis necessitates targeting these mechanisms. This article aims at discussing the pathogenesis and preventive measures of sepsis-induced acute kidney injury.

Keywords: *Acute kidney injury, prevention, sepsis.*

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INTRODUCTION:

Sepsis is a serious life-threatening complication of infection affecting about 38 to 110 per 100,000 individuals [1]. It refers to the host dysregulated response to infection leading to a life-threatening organ dysfunction, with a potential in-hospital mortality rate more than 10% [2]. Many risk factors are known to increase the incidence of sepsis and to worsens its outcome. Acute injury is one of the most common organ dysfunctions that results from sepsis and worsens its prognosis. Acute renal insult occurs in about 12% of patients with sepsis, and it results in significant mortality [3]. The in-hospital mortality rate among patients who develop acute kidney injury is as high as 50% [4]. Therefore, researchers were endeavouring to understand the aetiology, pathogenesis, and the preventive strategies of acute kidney injury among hospitalized patients with sepsis.

In patients with sepsis, acute kidney injury is considered an independent risk factor for mortality [5]. Thus, early identification and treatment of sepsis-induced acute kidney injury is fundamental for reduction of sepsis-associated mortality. Because proper prevention necessitates adequate understanding of the pathogenesis, this article aims at reviewing the pathogenesis and preventive measures of acute kidney injury in hospitalized patients with sepsis.

PATHOGENESIS OF SEPSIS-INDUCED ACUTE KIDNEY INJURY

Acute kidney injury is a commonly encountered among patients with sepsis and is considered a direct predictor of mortality. Therefore, it has been a subject of considerable research for decades. However, despite years of research, the exact pathophysiological mechanisms of sepsis are not completely clear.

Till the last decade, sepsis-induced acute kidney injury was thought to be due to hypoperfusion and ischemic injury to the kidney tissue. However, recent research did not show this was exactly correct. Many mechanisms were found to be involved in the development of acute kidney injury in cases of sepsis, namely: renal ischemia, inflammation, and body's adaptive response to tissue injury [6]. These three mechanisms will be reviewed in this section. Current evidence suggests that more than one single mechanism act simultaneously to result in acute kidney injury, and these mechanisms probably have a synergistic effect on each other and potentiate, accelerate and worsen kidney damage.

1. Renal ischemia:

Disturbance of renal microcirculation was the most common described pathophysiologic mechanism responsible for acute renal injury in sepsis. Sepsis results in a systemic inflammatory response reaction and generalized vasodilatation [7]. This lead to global ischemia to various organs ischemia and cellular damage. Kidneys are the most common organ affected by the generalized hypoperfusion with a resultant renal tissue ischemia and acute tubular necrosis (ATN) [8].

Though renal ischemia was thought to be the main cause of acute kidney injury in sepsis, many literature studies demonstrated that acute kidney injury could occur in cases of normal renal perfusion. Reduction in renal blood flow was not found to be a universal finding in all patients with sepsis-induced renal failure[9]. Furthermore, acute kidney injury was shown to occur in patients with mild and moderate sepsis before the stage of global ischemia occurs and in patients without hemodynamic instability. Thus, new mechanisms of sepsis were explored to explain the associated acute kidney injury.

2. Inflammation:

Ischemia was the second discovered pathophysiologic mechanism of sepsis-induced acute kidney injury. Researchers noted that certain cytokines (such as IL-6 and IL-10) were significantly correlated with the severity of the acute kidney injury [9]. Researchers proposed that infection stimulate a host response to get rid of the pathogenic organism. In spite of being beneficial in clearance of infection, this host response may also result in tissue injury. The infectious pathogens seem to interact with receptors in different tissues leading to activation of inflammatory cascade and up-regulation of transcription of genes included in inflammation[5]. The identified receptors involved in this process are toll-like receptors, nucleotide-binding oligomerization domain-like receptors, and retinoic acid inducible gene 1-like receptors [10,11]. In postmortem analysis of renal tissue, extensive tubular necrosis out of proportion and duration of the renal hypoperfusion was noted suggesting that renal damage had occurred long before reduction of renal blood flow [12]. Additionally, laboratory in vitro studies in patients indicated for renal transplantation demonstrated that adding plasma from patients with sepsis to a tube containing renal cells resulted in damage to these cells and destruction of their foot processes [13].

3. Adaptive tissue response to injury

The third proposed mechanism of acute kidney injury among sepsis patients is the cellular adaptive

response to tissue injury. When exposed to inflammation and ischemia, renal tubular cells react to these circumstances by downregulating their metabolism and sending signals to adjacent cells via their paracrine function to downregulate the renal cellular metabolism to protect against cellular apoptosis or necrosis. Mitochondria are the main intracellular organelles responsible for this adaptive response. They function maximally to utilize the existing energy maintain cell survival and prevent necrosis. This was proposed by researchers who visualized swollen mitochondria in renal tubular cells in patients with sepsis-induced acute kidney injury [14].

Under extreme oxidative stress, mitochondrial capacity to adapt to impending cellular damage fails and get damaged. The process of removal pf the damaged mitochondria, or mitophagy, becomes compromised under the effect of inflammatory mediators and reactive oxygen species. This reduced mitophagy is positively correlated with progressive renal injury [15]. Thus, areas of focal renal damage are maximum at regions of inflammation, oxidative stress, and hypoxemia [16].

PREVENTION OF SEPSIS AND TREATMENT STRATEGIES

Because acute kidney injury is associated with high mortality rates among patients with sepsis, early prevention of this condition is important. Understanding the pathophysiologic mechanisms of sepsis-induced acute kidney injury aided in establishment of management lines for prevention of this serious complication. Though no therapeutic agent or measure has been approved as a reliable preventive measure for acute kidney injury, some off-label measures are beneficial. For prevention of renal hypoperfusion, fluid resuscitation is essential. For prevention of inflammation-induced acute kidney injury, many agents are under investigations for early treatment of infection. This section will review the lines available for prevention of acute kidney injury in patients with sepsis.

4. Prevention of renal hypoperfusion and ischemia

Renal hypoperfusion resulting from microcirculatory dysfunction, as aforementioned, remains the main pathophysiological mechanism of acute kidney injury among patients with sepsis. For prevention of hypoperfusion, fluid volume should be monitored, renal blood flow should be increased, and the haemoglobin transferring oxygen and nutrition to the kidneys should be maintained at certain levels.

a) Maintaining fluid volume

Maintaining a proper fluid volume for perfusion of various organs and without causing an overload on cardiac and pulmonary function remains a major challenge for critical care physicians. Fluid resuscitation is fundamental for adequate renal perfusion in patients with sepsis. Under normal conditions, intravascular fluid volume is maintained by achieving a balance between intravascular and extravascular oncotic pressures. In sepsis, the intravascular oncotic pressure gets reduced due to the systemic inflammatory response [[17]. Therefore, uncalculated fluid administration may worsen the condition and accelerate kidney damage [18]. Initially, patients with sepsis-induced acute kidney injury should be treated with crystalloid rather colloid solution to avoid osmotic nephrosis [19]. Intravenous albumin administration was also shown to improve renal blood flow, reduce sepsis-induced acute kidney injury, and subsequently reduce the mortality [20]. Though this was thought to be due to increasing intravascular osmotic pressure, this mechanism has never been proven [21]. In advanced cases of fluid overuse, temporary use of continuous renal replacement therapy may be life-saving [22].

b) Improving renal blood flow

For improving renal perfusion, many vasodilator agents are tested in patients with sepsis to investigate their impact on renal blood flow. Examples of medications tested to vasodilate renal vessels and improve renal blood flow were nitro-glycerine, erythropoietin, and statins [5,23,24]. They were proposed as agents that would vasodilate renal vessels, reduce vascular permeability, or increase renal vasculature plethora [5]. However, none of these agents was proved to be an effective monotherapy for preventing or reducing sepsis-induced acute kidney injury. Currently, the only approved agents to enhance renal blood flow are vasopressin with norepinephrine through their vasodilator effect on renal vessels [25].

c) Maintaining hemoglobin level

Adequate haemoglobin is essential to carry oxygen and nutrition to various organs. Maintaining haemoglobin level at a certain value is known to be essential for cardiac and cerebral perfusion [17]. After cardiac surgery, the haematocrit value should be more than 24% to prevent post-surgical acute kidney injury [26]. Though no studies have proven the effect of maintaining a sufficient haematocrit level in preventing acute kidney injury in sepsis, this seems a promising field of research that may provide an inexpensive preventive measure for serious renal

damage.

5. Reduction of inflammation and adaptive tissue response to injury

When inflammation was discovered to be an early pathophysiologic mechanism of sepsis-induced acute kidney injury. Many researches were carried out to develop a medication that can stop the inflammation early in patients with sepsis and subsequently prevent the progression of the condition to acute kidney injury. Many preventive modalities were developed to reduce the cytokines, inflammatory mediators, oxidative stress, and maladaptive cellular response to injury. The main modalities developed for these purposes were hemadsorption, polymyxin B hemoperfusion, administration of exogenous alkaline phosphatase, and modulators of cytokines signalling[5]. Hemadsorption and polymyxin B hemoperfusion reduce the circulating inflammatory mediators and had shown promising results in prevention of sepsis-induced kidney injury [27,28]. Alkaline phosphatase is known for its endogenous detoxifying effect through dephosphorylation of proinflammatory mediators. In one study, exogenous alkaline phosphate was found to reduce reactive oxygen species and oxidative stress in renal tubules among patients with sepsis [29]. However, none of these factors was tested in large sample double-blinded randomized studies to approve its efficacy and effectiveness. Modulation of cytokine signalling is another mechanism under current research for prevention of inflammation-induced acute kidney injury [30].

CONCLUSION:

Understanding the pathogenesis is essential for proper prevention of sepsis-induced acute kidney injury. Although the details of the basic mechanisms of the condition remain elusive, some processes were discovered, and many advances were made. Sepsis-induced acute kidney injury occurs due to complex mechanisms that act synergistically to damage renal tissue. The main revealed mechanisms are microcirculatory dysfunction, systemic inflammation, and local maladaptive response of the renal tissue. Prevention of acute kidney injury among patients with sepsis necessitates targeting these mechanisms. Therefore, the main preventive lines are fluid resuscitation, improving renal blood flow, and administering agents that reduce systemic inflammation.

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REFERENCES:

1. Kempker JA, Martin GS. The Changing Epidemiology and Definitions of Sepsis. *Clin Chest Med*. 2016;37(2):165-179. doi:10.1016/j.ccm.2016.01.002
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama*. 2016;315(8):801. doi:10.1001/jama.2016.0287
3. Kaukonen K-M, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis. *N Engl J Med*. 2015;372(17):1629-1638. doi:10.1056/NEJMoa1415236
4. Wang HE, Muntner P, Chertow GM, Warnock DG. Acute kidney injury and mortality in hospitalized patients. *Am J Nephrol*. 2012;35(4):349-355. doi:10.1159/000337487
5. Zarbock A, Gomez H, Kellum JA. Sepsis-induced AKI revisited: pathophysiology, prevention and future therapies. *Curr Opin Crit Care*. 2014;20(6):588-595. doi:10.1097/MCC.0000000000000153.Sepsis-induced
6. Gomez H, Ince C, De Backer D, et al. A unified theory of sepsis-induced acute kidney injury: Inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. *Shock*. 2014;41(1):3-11. doi:10.1097/SHK.0000000000000052
7. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. *Nat Rev Dis Prim*. 2016;2. doi:10.1038/nrdp.2016.45
8. Prowle JR, Ishikawa K, May CN, Bellomo R. Renal blood flow during acute renal failure in man. *Blood Purif*. 2009;28(3):216-225. doi:10.1159/000230813
9. Le Dorze M, Legrand M, Payen D, Ince C. The role of the microcirculation in acute kidney injury. *Curr Opin Crit Care*. 2009;15(6):503-508. doi:10.1097/MCC.0b013e328332f6cf
10. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: Update on toll-like receptors. *Nat Immunol*. 2010. doi:10.1038/ni.1863
11. Takeuchi O, Akira S. Pattern Recognition Receptors and Inflammation. *Cell*. 2010. doi:10.1016/j.cell.2010.01.022
12. Murugan R, Karajala-Subramanyam V, Lee M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int*. 2010;77(6):527-535. doi:10.1038/ki.2009.502
13. Kruger B, Krick S, Dhillon N, et al. Donor Toll-

like receptor 4 contributes to ischemia and reperfusion injury following human kidney transplantation. *Proc Natl Acad Sci U S A*. 2009;106(9):3390-3395. doi:10.1073/pnas.0810169106
14. Zhan M, Brooks C, Liu F, Sun L, Dong Z. Mitochondrial dynamics: Regulatory mechanisms and emerging role in renal pathophysiology. *Kidney Int*. 2013. doi:10.1038/ki.2012.441
15. Sansanwal P, Yen B, Gahl WA, et al. Mitochondrial Autophagy Promotes Cellular Injury in Nephropathic Cystinosis. *J Am Soc Nephrol*. 2010. doi:10.1681/ASN.2009040383
16. Gatti S, Bruno S, Deregibus MC, et al. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. *Nephrol Dial Transplant*. 2011. doi:10.1093/ndt/gfr015
17. Honore PM, Jacobs R, Hendrickx I, et al. Prevention and treatment of sepsis-induced acute kidney injury: an update. *Ann Intensive Care*. 2015. doi:10.1186/s13613-015-0095-3
18. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care*. 2008. doi:10.1186/cc6916
19. Yunos NRAM, Bellomo R, Hegarty FC, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA - J Am Med Assoc*. 2012. doi:10.1001/jama.2012.13356
20. Caironi P, Tognoni G, Masson S, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock for the ALBIOS Study Investigators*. *N Engl J Med*. 2014. doi:10.1056/NEJMoa1305727
21. Kumar R, Kumar S, Lata S. Albumin infusion may deleteriously promote extracellular fluid overload without improving circulating hypovolemia in patients of advanced cirrhosis with diabetes mellitus and sepsis. *Med Hypotheses*. 2013. doi:10.1016/j.mehy.2012.12.039
22. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M. Renal replacement therapy in patients with acute renal failure: a systematic review. *JAMA*. 2008. doi:10.1001/jama.299.7.793
23. Boerma EC, Koopmans M, Konijn A, et al. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: A double-blind randomized placebo controlled trial. *Crit Care Med*. 2010. doi:10.1097/CCM.0b013e3181b02fc1
24. Song YR, Lee T, You SJ, et al. Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: A pilot study. *Am J Nephrol*. 2009. doi:10.1159/000223229
25. Russell JA, Walley KR, Singer J, et al. Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock. *N Engl J Med*. 2008. doi:10.1056/NEJMoa067373
26. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. *Ann Thorac Surg*. 2003. doi:10.1016/S0003-4975(03)00558-7
27. Cantaluppi V, Assenzio B, Pasero D, et al. Polymyxin-B hemoperfusion inactivates circulating proapoptotic factors. *Intensive Care Med*. 2008. doi:10.1007/s00134-008-1124-6
28. Kellum JA, Venkataraman R, Powner D, Elder M, Hergenroeder G, Carter M. Feasibility study of cytokine removal by hemoadsorption in brain-dead humans. *Crit Care Med*. 2008. doi:10.1097/01.CCM.0000291646.34815.BB
29. Heemskerk S, Masereeuw R, Moesker O, et al. Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients. *Crit Care Med*. 2009. doi:10.1097/CCM.0b013e31819598af
30. Wilson a G, Symons J a, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci U S A*. 1997. doi:10.1073/pnas.94.7.3195