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Review Article

Overview of sepsis associated acute kidney injury: literature review

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ABSTRACT

The incidence of acute kidney injury has been estimated to be around a fifth of the adult patients during their hospital stays. Sepsis is estimated to be the commonest cause for AKI development in critically-ill patients; contributing to the pathology in 20-50% of the cases. We reviewed some aspects of sepsis-associated AKI. Among the risk factors that may contribute to the development of AKI, age, sex, and the presence of comorbidities as diabetes, heart, and liver diseases were reported as significant factors associated with the development of the condition. The pathophysiology of sepsis-induced AKI is still unclear; however, some authors said that it may be related to the hypoperfusion of the renal tissue and subsequently induced ischemia. This theory was supported by animal studies; however, other investigations on humans reported no association between the two events. On the other hand, we believe that sepsis-induced AKI is probably due to the associated severe inflammatory state and hemodynamic instability are the main accusants. The management of this condition requires early diagnosis and early intervention by managing sepsis. Moreover, vasopressors as epinephrines have proved efficient in managing the shock state, even better than renal replacement therapy.

Keywords: Sepsis, Acute kidney injury, Inflammation

INTRODUCTION

The incidence of acute kidney injury (AKI) has been estimated to be around a fifth of the adult patients during their hospital stays. Moreover, it has been estimated that around 50% of critically-ill patients are affected by AKI morbidity.[1,2] The prognosis of AKI is usually bad when associated with other comorbidities which is the case with critically-ill hospitalized patients.[3-6] Moreover, mortality records from this phenomenon have been estimated at 20-40% rates attributable to the underlying disorder.[7,8] In these patients, the etiology behind the development of AKI usually attributes to major surgeries, hypovolemia, iatrogenic nephrotoxicity, and sepsis.[7]

Sepsis is estimated to be the commonest cause for AKI development in critically-ill patients; contributing to the pathology in 20-50% of the cases. Although sepsis is estimated to be the commonest cause for developing AKI, AKI attributable to other etiologies have been also associated with the development of sepsis.[9] The co-occurrence of AKI and sepsis in these patients also increases the risk of in-hospital mortality by 6-8 folds higher than usual.[3,10] Besides, chronic renal failure is also a risk co-morbidity in patients that were not complicated by AKI in the first place.[11] Despite these important statistics, the mechanism behind which sepsis induces AKI is still unknown, and accordingly, the therapeutic approaches remain symptomatic and non-specific. However, previous theories suggested that AKI is attributable to the hypoperfusion state that may be caused by sepsis. However, investigations proved that this theory is redundant. For instance, Prowle et al reported that no significant reduction in the renal blood flow (RBF) was noticed with patients that developed sepsis-induced AKI.[12] Similarly, Langenberg et al conducted an animal study and reported that the incidence of sepsis-associated AKI occurred despite normal or increase RBF.[13] In the same context, Murugan et al estimated that nearly 25% of their included population did not suffer from events attributable to hypoperfusion as pneumonia, hypotension, and were never in an ICU, which proves that sepsis-associated AKI is not attributable to hypoperfusion.[14]

Investigations showed that sepsis-associated AKI is mainly characterized by the presence of focal tubular injuries with no true or minimal cell death.[15,16] Other characteristics by which sepsis may induce organ damage include the presence of diffuse abnormalities in the microcirculation, inflammation, and cellular response to the injury. These factors are present regardless of the organs affected, staging and severity of the lesions, and the species.[17-19] In this review, we aim to shed more light on many aspects of sepsis-associated AKI from previous studies found in the literature.

An extensive literature search of the Medline, Cochrane, and EMBASE databases was performed on 9 November 2020 using the medical subject headings (MeSH) or a combination of all possible related terms. Papers discussing the aspects of sepsis-associated AKI were screened for relevant information. Any limits on date, language, and age of participants or publication type were not posed.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF SEPSIS ASSOCIATED AKI

Many risk factors for developing AKI have been previously reported. To assess the reliability of these factors, we reviewed some studies which considered the inclusion of patients with normal kidney function tests for better assessment of the risk factors. Previous studies showed that age, sex, and race are significant risk factors that may contribute to the pathophysiology of AKI.[20-22] Chronic kidney disease has been also marked as a significant risk factor, as Pannu et al showed that the risk of developing AKI increased as the glomerular filtration rate decreased.[23] Moreover, the authors reported that this finding was also associated with the severity of the injury and mortality from the lesion. Bagshaw et al also reported that diabetes mellitus was a significant risk factor in their population for developing a stage III AKI; Odds ratio (OR) 10.3; 95%, confidence interval (CI); 7.7-13.6 and subsequent mortality (OR: 1.2; 95% CI: 1.2-1.7). Hypoalbuminemia (<1 g/dl) was also reported as a risk factor by various studies in the literature.[25,26] An underlying chronic liver disease (OR: 2.18; 95 CI: 1.16-4.1), and liver cell failure (OR: 1.9; 95% CI: 1.34-2.71) were also reported as significant risk factors that may contribute to the development of AKI following sepsis as reported by de Mendonca et al and Chertow et al respectively.[20,21] Other risk factors include heart failure and other cardiovascular diseases, in addition to being on mechanical ventilation.[20,22,24,27] Moreover, sepsis was also reportedly associated with increased rates of deaths from AKI.[21]

AKI is a frequent complication in hospitalized patients, especially those in the ICU, and having sepsis makes the incidence of developing AKI even greater. A multicenter study conducted by Uchino et al reported that the incidence rate could be up to 47.5% which can lead to a high mortality rate in these patients as 60% of the sepsis-induced AKI patients were dead.[7] Another multi-center Chinese study conducted by Jiang et al reported an incidence rate of 51% in sepsis patients that were admitted to the ICU.[28] The authors also reported that most of these patients developed AKI on the 4th day of hospital stay. On the other hand, previous investigations also showed that AKI can also increase the risk of developing sepsis. Mehta et al reported that after five days of having AKI, 40% of their patients developed sepsis.[29] These high rates indicate the fact that sepsis-induced AKI is a common disorder and are both independently associated, and therefore, interventional approaches should be conducted. For proper intervention, early detection and diagnosis have been reported to be crucial in achieving better diagnostic outcomes and consequently enhancing the prognosis of the disorder.[30-32]

The pathophysiology of sepsis-associated AKI has been controversial and vague for a long time. However, recent approaches have provided useful information in the field which may have made it closer to a better understanding.[33-35] Studies showed that reduced renal perfusion and ischemia may contribute to the lesion, and are even considered the primary factors behind the development of AKI. However, this theory was not always validated as discussed before, and new evidence shows that inflammation and subsequent cell apoptosis are also contributing agents.[36,37] These reports are logical as tissue inflammation and microvascular complications have been associated with sepsis-associated end-organ failure. Tissue inflammation induced by sepsis might

involve the release of many cytokines and acute phase reactants that may contribute to the pathology. For instance, nitric oxide, and reactive oxygen species have been described to be playing a role in end-arterial thrombosis and endothelial damage.[38-41] An *in vitro* study conducted by Langenberg et al showed that sepsis-associated AKI induced a state of inflammation with patchy changes, but with a limited renal tubular injury.[36] Moreover, the authors found that animals with sepsis-associated AKI showed higher RBF rates. On the other hand, previous studies on humans showed that RBF was much reduced and therefore, it was thought to be the main contributing factor.[42-44] These different findings between animal and human studies indicate the need for further comparative studies and also necessitates the need for more histological examination of the affected kidneys for better examination and diagnosis.

REPORTED MARKERS IN SEPSIS-ASSOCIATED AKI

Previous studies showed that many markers have been associated with the development of AKI that is attributable to sepsis. These markers have been divided into; metabolomics, standard and serum biomarkers, urinary markers, experimentally associated markers and microRNAs (mRNAs).[45] In general, the diagnosis of AKI is based on the presence of elevated levels of serum urea and creatinine, in addition to the urine output of the patients. Kashaki et al have also reported the presence of other markers that are associated with AKI diagnosis.[46] These include cystatin C, neutrophile gelatinase-associated lipocalin (NGAL), kidney injury molecule -1 (KIM-1), urinary insulin like growth factor binding protein-7 (IGFBP-7), interleukin 18 (IL-18), interleukin 18 (IL-18), urinary tissue inhibitor of metalloproteinase 2 (TIMP-2), urine angiotensinogen, calprotectin, and liver fatty acid-binding protein.[46] The presence of these biomarkers may help in the early detection of renal injury, and consequently, the early initiation of therapeutic modalities for better prevention of complications and chronicity. Among the previously mentioned biomarkers, Klein et al conducted a meta-analysis to find the most significant risk biomarkers associated with AKI.[47] The authors reported that in 15,928 patients with critical AKI injuries, the most significant biomarkers were serum NGAL, cystatin C, and urinary TIMP-2 and IGFBP-7. Although these markers have been proven to be associated with AKI and might be considered as sensitive agents for early detection of the lesion, the diagnosis, and initiation of therapy are not dependant on them, but also other clinical and laboratory markers. The creatinine clearance test has been the most sensitive factor for diagnosis of AKI and initiation of therapy. Therefore, these biomarkers should be reconsidered with other clinical and laboratory features when applied clinically.[48] Previous animal model studies have also shown that sepsis-associated AKI is related to the presence of metabolomic markers. These include N-acetylglutamine, lactate, alanine, myoinositol, pyruvate, glutamine, glucose, valine, ascorbic acid, N-acetylaspartate aminoadipic acid, and betaine in addition to other markers that has been found to be correlated with NGAL, and serum creatinine.[49] Additional various findings have been also associated with the different forms of AKI. These include mesangial cells, podocytes, tubular cells, endothelial cells, fibroblasts, macrophages. Besides, HSP70, HSP27, HSP47, HSP90, HSP60, and HSP32 have been also expressed.[50] A previous investigation showed that HSP 72 was also significantly elevated in the first three days of AKI in 30.4% of their population.[51] Additionally, miRNAs have been also reported to be associated with tissue inflammation and apoptosis in AKI. These include; miR-9, miR-15a, miR-16, miR-146 a/b, miR-223, miR-155, miR-203, miR-126, and miR-199a.[52,53] These agents are supposed to play important roles against tissue inflammation and proliferation, however, they may lead to serious side effects as vascular complications, and cellular apoptosis.[50]

THERAPEUTIC AND INTERVENTIONAL APPROACHES IN SEPSIS-ASSOCIATED AKI

Kellum et al said that preventing sepsis-associated AKI from developing in nearly impossible as most patients would have developed during hospitalization at presentation.[54] Therefore, it is recommended that sepsis treatment should be inaugurated as early as possible using suitable antibiotics that can enhance the prognosis of the condition and intervene against the development of sepsis-associated severe complications including AKI. Bagshaw et al showed that delaying the treatment of sepsis with antibiotics significantly increased the risk of developing early AKI.[55] On the other hand, other conditions should be considered when choosing the appropriate treatment for sepsis. For instance, nephrotoxic agents, like vancomycin, aminoglycosides, amphotericin B, and radiocontrast substances, should be avoided or used with caution to prevent the deterioration of the kidney functions. Accordingly, the limited use of these agents should be approached with caution and with continuous monitoring. Renal replacement therapy (RRT), and vasopressins have been also described in the literature as preventive measures that main intervene against the bad prognosis of the kidney lesions. Rhodes et al recommended the use of norepinephrine for the management of septic shock, and therefore, reduce the complications as AKI.[56] On the other hand, previous investigations showed that dopamine should not be used as a reno-protective modality in septic shock patients due to the remarkable adverse effects it can produce, unlike norepinephrine which possesses less frequent side events.[56-59] Moreover, Gordon et al in a clinical trial concluded that using vasopressin therapy significantly lowered the need to conduct RRT.[60] Using pharmacological modalities is usually preferred over invasive procedures which frequently lead to the development of serious side effects and may aggravate the condition. Moreover, the timing of conducting RRT has been controversial among studies in the literature.

Some observational studies showed that early conduction of the modality can decrease the severity of AKI while other randomized trails showed that no association was found. Therefore, it has been concluded that adequate conservative and symptomatic treatment can dispose of the need to conduct RRT modalities.

After the treatment of sepsis by suitable antibiotics, physicians should immediately start treating AKI and other conditions that may affect the prognosis. Early treatment modalities include caring for fluids and volume status of the patient that is sufficient enough to achieve adequate perfusion of the kidney, for it to heal.[56] Moreover, this step should be done carefully to avoid hypervolemia and the development of other severe, and unnecessary complications. This can happen following the previous AKI-induced plasma protein loss, and increased capillary permeability which attributes for the accumulation of fluids in the body and developing complications. Specifically, in the renal parenchyma, fluid overload can increase the venous pressure reducing renal perfusion and glomerular filtration rate, which may lead to further accumulation of fluids from AKI-induced renin secretion and salt and water retention. Therefore, it has been agreed that the appropriate use of fluid resuscitation with continuous monitoring of the patient's hemodynamics should be approached carefully for obtaining better outcomes. Saline and crystalloid solutions have shown favorable outcomes, while gelatine and hydroxyethyl starches have been associated with increased risk of sepsis-induced AKI. Other reported pharmacological modalities include the use of alkaline phosphatase which is a human-recombinant subject designed to mimic an endogenous enzyme that may play a role in protecting the kidneys against the manifestations of sepsis. Moreover, angiotensinogen II has been reported to increase the glomerular filtration rate and enhance the nourishment of both kidneys.

CONCLUSION

In this review, we summarized some of the aspects of sepsis-associated AKI including the demographics, risk factors, pathophysiology, prevention, and treatment. We recommend that further studies should be conducted for better management of the condition as the risk of mortality might be high. Moreover, early management of sepsis should be approached by clinicians to prevent any complications as AKI. Moreover, many markers have been found as good and early indicators of AKI, however, these can be used solely due to the presence of more sensitive agents as creatinine clearance. Additionally, previous studies showed that conservative treatment might be more effective than RRT in attaining better clinical outcomes and avoiding side effects.

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