Review Article

Sepsis-associated Acute Kidney Injury, Diagnosis, and Management, Review Article

Abdullah Mohammed Alghamdi[1*], Assem Mohammed Alghamdi[2], Saif Awadh B Alsemairi[2], Abdulaziz Abdullah Alangari[2], Mahmoud Abdullah Alabbad[3], Ebaa Ali Alebrahim[4], Rawan Ahmad Albluwi[4], Abdulrahman Ibrahim Almaymn[5], Abdulrhman Mahbob Alawfi[6], Hayder Saleh Alkhanjaf[6]

[1]*Faculty of Medicine, Baha University, Baha, KSA.*
[2]*Faculty of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA.*
[3]*Faculty of Medicine, Hereditary Blood Diseases Center, Alahsa, KSA.*
[4]*Faculty of Medicine, Arabian Gulf Medical University, Manama, Bahrain.*
[5]*Faculty of Medicine, Imam Mohammed Bin Saud Islamic University, Riyadh, KSA.*
[6]*Faculty of Medicine, Taibah University, Madinah, KSA.*

Email: *Bin.Zw7@yahoo.com*

ABSTRACT

Sepsis-associated acute kidney injury (S-AKI) is a common condition found in critically ill patients that raises morbidity as well as mortality risk. Clinical and fundamental science data suggests that S-AKI is different from AKI without sepsis since it is characterized by a variety of discrete pathophysiological processes, a distinct timing profile regarding the onset or the duration, and different short- and long-term results. Physicians must have a thorough grasp of S-AKI to establish adequate diagnosis and treatment methods. To review the published literature and provide adequate coverage of S-AKI, diagnosis, and management. For articles' selection, the PubMed search engine was used, and the following keywords were used in mesh (("Sepsis-associated acute kidney injury"[Mesh]) AND ("diagnosis"[Mesh]) OR ("management"[Mesh])). AKI's early detection in the presence of sepsis is critical for providing the best care and preventing additional kidney damage. Detecting AKI in the context of infection is very important since it might indicate sepsis in a patient. Injury or stress indicators combined with functional assessments may give more information than each one alone. After many types of research including large numbers of patients and randomized controlled trials (RCTs) of particular treatments, early diagnosis, fast fluid resuscitation, and early antibiotic administration remain the only interventions that improve sepsis outcomes. Fluid resuscitation alone is insufficient to provide appropriate renal perfusion pressure, thus, patients with sepsis frequently require vasopressor assistance.

Key words: *Sepsis-associated acute kidney injury, Diagnosis, Management, Evaluation*

INTRODUCTION

S-AKI is a frequent complication in hospitalized and critically ill patients that raises the risk of chronic complications and has a high death rate [1]. Sepsis and AKI make the body susceptible to each other as separate illnesses. Sepsis causes 26 to 50% of all AKI in adults and children in industrialized countries, compared to 7 to 10% of AKI caused by primary renal disease. Despite that sepsis is the most prevalent cause of AKI, any AKI has a greater risk of developing sepsis [2-4]. Nevertheless, AKI may increase susceptibility to a higher risk of sepsis,

according to observational evidence. 243 (40%) patients in the Program to Improve Care in Acute Renal Disease (PICARD) trial had sepsis five days after developing AKI [4].

Clinical and fundamental science data suggests that S-AKI is different from AKI without sepsis since it is characterized by a variety of discrete pathophysiological processes, a distinct timing profile regarding the onset or the duration, and different short- and long-term results [5-7]. In sepsis, determining the exact beginning of harm is almost impossible, making immediate intervention to prevent renal injury is challenging. Given the overall and pervasive effects of AKI and sepsis, physicians must have a thorough grasp of S-AKI to establish adequate diagnosis and treatment methods. Therefore, we aim in this review to provide adequate coverage of S-AKI, and its different aspects.

MATERIALS AND METHODS

PubMed database was used for articles selection, and the following keys were used in the mesh (("Sepsis-associated acute kidney injury"[Mesh]) AND ("diagnosis"[Mesh]) OR ("management"[Mesh])). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics: Sepsis-associated acute kidney injury, diagnosis, and management. Exclusion criteria were all other articles, which did not have one of these topics as their primary endpoint.

RESULTS AND DISCUSSION

The incidence and trend of AKI associated with sepsis have proven challenging to adequately measure. Even though screening programs and data analytics are aiding in the diagnosis of AKI linked with sepsis, identifying AKI as being related to sepsis remains difficult due to the various variables that are common in critically sick patients. The most common pre-morbid risk factors for AKI include chronic kidney disease (CKD), advanced age, and cardiovascular illness [8, 9]. Cardiovascular failure, sepsis, and liver failure were all linked to the most common acute disease linked to AKI [10].

Sepsis is one of the most common causes of serious disease [11]. The prevalence of sepsis, also known as septic shock, is high and rising. In the United States, it has been revealed that there is an 8.7% yearly rise in sepsis diagnoses over 22 years [12]. Between 2004 and 2009, the yearly incidence of severe sepsis increased by 13% on average [13]. Although the overall sepsis-related death rate is declining (currently ranging around 18%–25%), the standardized mortality rate for septic patients remains substantially higher than the general intensive care unit (ICU) standardized mortality ratio [14]. The rate of sepsis and accompanying morbidity appears to be increasing, but the death rate of sepsis patients appears to be decreasing. According to a study of 750 million hospital admissions in the United States from 1979 to 2000, sepsis rose from 82.7 to 240.4 per 100,000 people, a yearly rise of 8.7%. In-hospital death rate has decreased from 27.8% to 17.9% [11, 15].

Furthermore, worldwide estimates show that sepsis's consequences are considerable, including all elements of ICU-related morbidities, such as increased duration of stay, ventilation, secondary infections, and death, as well as long-term survival concerns [15]. After many types of research including large numbers of patients and RCTs of particular treatments (e.g., activated protein C), early diagnosis, fast fluid resuscitation, and early antibiotic administration remain the only interventions that improve sepsis outcomes [11].

Pathophysiology

Although the specific pathophysiology of sepsis-induced AKI is uncertain, a multi-pronged damage mechanism is largely considered. This kind of AKI includes direct inflammatory tissue damage, ischemia-reperfusion injury, coagulation, and, apoptosis and endothelial cell dysfunction [16, 17]. Furthermore, we can assume that sepsis-induced AKI has different pathophysiologic processes than non-septic AKI based on recent findings [18]. This would take into account the fact that sepsis-induced AKI may necessitate a variety of treatments. Regardless of the kind of infecting bacteria, a high plasma concentration of endotoxin (lipopolysaccharide; LPS) is routinely identified in the systemic circulation during sepsis, most likely as a result of LPS translocation from the gut's native Gram-negative flora [19].

LPS, cytokines, and finally nitric oxide are produced as a result of sepsis' inexorable downward spiral. The growth and death of Gram-negative bacteria lead to the release of LPS into the circulation and fast dispersion throughout the body, in addition to the intestinal-derived LPS translocation that happens with any kind of sepsis. The LPS-binding protein binds to the physiologically active component lipid A of LPS (LBP). The LBP-LPS complex interacts with the cell membrane Toll-like receptor 4-MD-2 complex on neutrophils, macrophages, and

monocytes, but it also attaches to other cells, including renal tubular epithelial cells [16, 20]. These cells are subsequently induced to generate cytokines, both MyD88-dependent, and non-MyD88-dependent. MyD88b is considered to have a major role in the development of septic AKI [21].

The proinflammatory cytokines generated by LPS exposure, such as interferon (IFN), interleukin (IL)-1, and tumor necrosis factor (TNF), bind to different receptors on different cell types. TNF receptor 1 is present on glomerular endothelial cells in the kidney, whereas TNF receptor 2 is found on renal tubular epithelial cells [22]. The transcription of the inducible nitric oxide synthase (iNOS) gene, translation of iNOS mRNA, and subsequent assembly of the iNOS protein result in the production of nitric oxide after a series of events. Septic shock is caused by the creation of high quantities of nitric oxide during sepsis, which causes systemic vasodilation. Baroreceptors detect the resulting arterial volume loss, which results in angiotensin production and increased sympathetic activity. Intra-renal vasoconstriction occurs, resulting in salt and water retention and a decrease in glomerular filtration rate (GFR) [23].

In sepsis-induced AKI, neither systemic nor intra-renal hemodynamic instability is the main culprit. In reality, hemodynamic variables do not appear to be very important, since hypotension in critically sick patients with severe sepsis does not correlate with AKI [16]. Systemic inflammation may cause renal tubular damage by producing cytokines and oxygen free radicals [23]. As a result, despite the etiology of sepsis-induced AKI being multifactorial and not entirely understood, nitric oxide is thought to play a significant role in the process [24].

An elevated serum creatinine concentration and/or a reduction in urine output are presently used to diagnose AKI. Serum creatinine, like other types of AKI, can be an insensitive indicator of kidney damage, and oliguria in S-AKI can be vague. However, in sepsis, oliguria appears to be more important, and a connection between oliguria and AKI may be evident even after 3 to 5 hours [25]. Many patients' serum creatinine levels are further limited by the lack of a baseline value, and there is no consensus on how to handle this missing data [26].

Sepsis and Septic Shock: Third International Consensus Definitions (Sepsis-3) was recently suggested [27]. As a result, S-AKI is sometimes referred to as AKI in the sepsis setting without any significant contributing factors, or AKI with both Kidney Disease and Sepsis-3: Improving Global Outcomes (KDIGO) criteria present at the same time [28].

In clinical practice, it is typically difficult to validate urine output criteria outside of the ICU. In patients with AKI, continuous urine output monitoring is related to (although not always directly linked to) improved survival results. Up to one year after AKI has occurred, urine output continues to play an important role in predicting short- and long-term outcomes.

Patients with severe AKI who met both the urine and serum creatinine output criteria received the most RRT in the hospital, had the longest ICU and hospital stays, and had the highest rates of death [29]. Yet, there are many drawbacks to using urine and serum creatinine output to diagnose AKI [1].

Sepsis lowers muscle perfusion and, as a result, creatine generation, slowing the rise in blood creatinine levels and making early diagnosis of AKI difficult. Furthermore, AKI may be underdiagnosed as a result of dilutional effects caused by vigorous fluid resuscitation in septic shock. Diuretic medication may restrict the utility of oliguria and other urine indicators for AKI diagnosis, even though loop diuretics require intact tubular function to perform well [30]. The establishment of a baseline serum creatinine is the first disadvantage of a criterion that depends on the change in serum creatinine [10]. In the absence of prior results, there is no accepted technique for determining pre-AKI baseline blood creatinine [31].

Furthermore, due to renal reserve and the kinetics of AKI, increases in serum creatinine are frequently delayed. Urine production is insensitive, and it is usually only monitored correctly in the ICU. Several retrospective cohort studies have discovered that the same stage of AKI, as measured by blood creatinine and urine output, is linked to different risks. Isolated urine output-based AKI is linked with a greater risk of morbidity and mortality as compared to no AKI, however, these risks are lower than those associated with serum creatinine-based AKI [10, 32].

One of the most used traditional approaches for detecting kidney dysfunction is urine microscopy. When compared to patients with AKI from other causes, S-AKI patients exhibited higher urine microscopy scores. Urine microscopy was highly specific but ineffective in detecting increasing AKI, with sensitivity and specificity of 67% and 95% for severe cases. As a result, while urine sediment can assist in determining the etiology of AKI and give prognostic information, it has low sensitivity for detecting AKI and its poor prognosis [1].

S-AKI Biomarkers

Early detection of AKI in the presence of sepsis is critical for providing the best care and preventing additional kidney damage. Detecting AKI in the context of infection is very important since it might indicate sepsis in a patient. Injury or stress indicators combined with functional assessments may give more information than each one alone [33].

Neutrophil gelatinase-associated lipocalin (NGAL) has been thoroughly studied in a variety of AKI phenotypes. Activated neutrophils and a variety of epithelial cells, including renal tubular epithelial cells, release NGAL (TECs). Preliminary studies showed that NGAL had a high sensitivity for predicting AKI, as well as being a useful predictive tool for RRT demand and in-hospital death [34]. Individuals with S-AKI had greater detectable NGAL levels in their plasma and urine than patients that have AKI due to other causes. In individuals with S-AKI, plasma NGAL proved to be beneficial in the prediction of renal function improvement at hospital discharge. Non-renal causes should be considered when interpreting NGAL in patients with sepsis [35]. Plasma NGAL levels may rise as a result of systemic infection and inflammation, even if there is no indication of AKI. In other trials, NGAL failed to distinguish between individuals with AKI and those who were not in the context of sepsis. Low sensitivity and specificity made it difficult to differentiate AKI from CKD using NGAL [36].

Another kidney injury biomarker is urinary kidney injury molecule-1 (KIM-1), which is increased in renal proximal TECs following ischemia and nephrotoxic lesions. According to a meta-analysis, urine KIM-1 is a good predictor of AKI (area under the curve of 0.86, specificity of 86%, sensitivity of 74%) [37]. There is a limitation of data on KIM-1, which is especially utilized for S-AKI. The area under the curve for utilizing urine KIM-1 at 24 hours for predicting early AKI in patients with sepsis was 0.91, and non-survivors had substantially higher urinary KIM-1 levels at 24 and 48 hours, according to one perspective research [10].

After hypoxic shocks, the cytoplasmic region of proximal TECs has flooded with urine liver-type fatty acid-binding protein. In those with S-AKI, non-survivors showed significantly higher levels of urine liver-type fatty acid-binding protein upon admission than survivors [38].

Urinary regulatory proteins [TIMP-2 and IGFBP7] are engaged in G1 cell cycle arrest, which is a protective strategy during cellular stress. In a validation trial with 728 patients, the urine [TIMP-2 and IGFBP7] product outperformed other biomarkers that are for predicting AKI, with an area under the curve of 0.80 [39]. The results of two further validation experiments had consistent outcomes. Non-renal organ failures in sepsis did not result in elevated [IGFBP7 and TIMP-2], unlike many other biomarkers. In the USA, the European Union, and other areas of the world, a test assessing urine [TIMP-2 and IGFBP7] has received regulatory clearance for AKI risk stratification [10].

Management

Fluids use

Conventional thinking holds that intensive fluid treatment is essential for effective sepsis and AKI management [40]. Hypoperfusion may not be present in septic AKI, as previously mentioned. As a result, vigorous fluid administration may be biologically irrational and unproductive; it may lead to renal edema, which can cause congestion and ischemia in an encapsulated organ [41].

Fluid retention in septic patients is probable as a result of fluid bolus treatment (FBT) associated with the oliguria of AKI [42].

In both the PICARD and the Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock groups, fluid accumulation led to poor outcomes and increased death rates, with persistent and widespread data demonstrating harm in a variety of patient populations, including those with septic AKI [41, 42].

In severe sepsis, a delayed positive fluid balance is a significant risk factor for death. This, however, is not linked to either protection against or danger of AKI [43]. This was recently validated in a retrospective examination of S-AKI, which included determining fluid balance at the beginning of organ failure, the initiation of vasopressors, and the diagnosis of sepsis [40].

Antibiotics use

Antimicrobial risk-benefit assessments may need to incorporate renal outcome in the setting of S-AKI, it is becoming evident. This was recently demonstrated by a retrospective review of 1,159 patients undertaken in Germany, which found that administering vancomycin in patients with S-AKI increased the chance of a prolonged need for RRT following ICU discharge [44].

Furthermore, bactericidal antibiotic usage has been linked to a transitory deterioration of renal function and an increase in inflammation during the acute phase [45]. However, a decreased incidence of AKI has been linked to early and adequate antimicrobial therapy, as well as septic source management. The risk of AKI rose by around 40% for every hour when proper antibiotic treatment was delayed. Furthermore, early antimicrobial treatment was linked to a higher chance of renal recovery within 24 hours [42, 46].

Vasopressor use

Maintaining an appropriate mean arterial pressure of 65 mmHg in a patient without prior hypertension in the setting of a full intravascular volume assists in optimal end-organ perfusion. Furthermore, recent sepsis recommendations prefer to give noradrenaline initially, then vasopressin. In comparison to noradrenaline, it is thought that vasopressin induces less tubular apoptosis, systemic inflammation, and kidney injury [47]. The vasopressin group had lower total pressor needs and required less RRT, but there was no difference in the key endpoint, the number of renal failure-free days as determined by stage 3 AKI, according to recent scientific gatherings [40].

It is impossible to overestimate the importance of maintaining renal perfusion pressure. Because fluid resuscitation is insufficient for achieving adequate renal perfusion pressure, patients with sepsis typically require vasopressor therapy. Norepinephrine appears to be the drug of choice when the volume and cardiac output have been stabilized but considerable vasodilation is preventing the accomplishment of appropriate renal perfusion pressure. Despite fears that norepinephrine's vasoconstriction might result in reduced renal perfusion and decrease of renal function, the contrary has been proved, and norepinephrine is now regarded as first-line therapy for hypotension in sepsis [48].

Vasodilation occurs in septic shock via several mechanisms, including increased nitric oxide production, and maybe hyporesponsive to catecholamines. Adrenoceptor downregulation can also be caused by excessive levels of exogenous and endogenous catecholamines. Due to abnormally low levels of endogenous vasopressin, exogenous vasopressin and its counterparts have been recommended as a therapy for septic shock.

Vasopressin's use resulted in improved urine output, a 75% increase in creatinine clearance, and a reduction in overall pressor need in a small, pilot, randomized, controlled trial of 24 patients with severe septic shock, while the comparator arm of norepinephrine had no positive advantage [49]. Despite finding a lower death rate in patients with less severe sepsis in the Vasopressin and Septic Shock Trial, there was no difference in the incidence of AKI or the requirement for RRT when vasopressin was used [50].

Renal replacement therapy

Treatment for S-AKI has included RRT. Although the timing of RRT starting is debatable, some retrospective data show that starting RRT before the development of overt AKI symptoms and the accumulation of a considerable quantity of fluid overload is linked to a higher chance of survival [11, 51].

It is still unclear how to effectively assist severely unwell septic individuals with AKI., Continuous renal replacement therapy (CRRT) is most typically employed in unstable critically ill patients because of its enhanced physiologic and hemodynamic homeostasis management and flexibility to the patient's condition. Although there is no clear evidence that one modality has a survival benefit, current results suggest that early CRRT assistance may help patients improve renal function faster and minimize their long-term risk of acquiring CKD [52, 53].

Despite early findings from Ronco *et al*. showing a possible advantage from higher-intensity dose dialysis (35–45 mL/kg/h), two large multicenter RCTs found no additional benefit of higher-intensity dose RRT compared to lower-intensity dose RRT, with less metabolic problems [54-56]. Furthermore, there was no significant difference in death odds ratios between patients with sepsis who got higher-intensity RRT versus those who received lower-intensity RRT [11, 55, 56].

CONCLUSION

AKI's early detection in the presence of sepsis is important for providing the best care and preventing additional kidney damage. In the context of infection, detecting AKI is very important since it might indicate sepsis in a patient. Injury or stress indicators combined with functional assessments may give more information than each one alone.

After many types of research including large numbers of patients and RCTs of particular treatments, early diagnosis, fast fluid resuscitation, and early antibiotic administration remain the only interventions that improve

sepsis outcomes. Fluid resuscitation alone is insufficient to provide appropriate renal perfusion pressure, thus, patients that have sepsis frequently require vasopressor assistance. Treatment for S-AKI has also included RRT. Starting RRT before the development of overt AKI symptoms and the accumulation of a considerable quantity of fluid overload is linked to a higher chance of survival.

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