Chapter

Sepsis Associated Acute Kidney Injury

Titik Setyawati, Ricky Aditya and Tinni Trihartini Maskoen

Abstract

AKI is a syndrome consisting of several clinical conditions, due to sudden kidney dysfunction. Sepsis and septic shock are the causes of AKI and are known as Sepsis-Associated AKI (SA-AKI) and accounted for more than 50% of cases of AKI in the ICU, with poor prognosis. Acute Kidney Injury (AKI) is characterized by a sudden decline in kidney function for several hours/day, which results in the accumulation of creatinine, urea and other waste products. The most recent definition was formulated in the Kidney Disease consensus: Improving Global Outcome (KDIGO), published in 2012, where the AKI was established if the patient's current clinical manifestation met several criteria: an increase in serum creatinine levels ≥0.3 mg/dL (26.5 μmol/L) within 48 hours, an increase in serum creatinine for at least 1.5 times the baseline value within the previous 7 days; or urine volume ≤ 0.5 ml/kg body weight for 6 hours. The AKI pathophysiology includes ischemic vasodilation, endothelial leakage, necrosis in nephrons and microtrombus in capillaries. The management of sepsis associated with AKI consisted of fluid therapy, vasopressors, antibiotics and nephrotoxic substances, Renal Replacement Therapy (RRT) and diuretics. In the analysis of the BEST Kidney trial subgroup, the likelihood of hospital death was 50% higher in AKI sepsis compared to non-sepsis AKI. Understanding of sepsis and endotoxins that can cause SA-AKI is not yet fully known. Some evidence suggests that renal microcirculation hypoperfusion, lack of energy for cells, mitochondrial dysfunction, endothelial injury and cycle cell arrest can cause SA-AKI. Rapid identification of SA-AKI events, antibiotics and appropriate fluid therapy are crucial in the management of SA-AKI.

Keywords: Sepsis, Acute kidney injury

1. Introduction

Acute Kidney Injury is a syndrome that consists of several clinical conditions, due to sudden kidney dysfunction (within a few hours to several days) that causes retention of residual nitrogen (urea-creatinine) and non-nitrogenous metabolism, with or without oligouria, and is affected by some underlying disease. The most common causes of AKI in patients with critical illness are sepsis and septic shock, accounting for more than 50% of AKI cases in the ICU. The incidence of sepsis and AKI in critical patients increases gradually and both shows poor prognosis. In various epidemiological studies, it is said that AKI occurs in 11-60% of sepsis patients, 23% of severe sepsis patients and 51 – 64% in septic shock patients [1, 2]. Sepsis is one of the causes of Acute Kidney Injury (AKI) in critically ill patients treated in the ICU known as Sepsis-Associated AKI (SA-AKI). The morbidity and mortality

rate of SA-AKI is still quite high even though the development of supportive care technology has progressed. A good understanding of SA-AKI is expected to increase alertness and make appropriate decisions in initiating management so as to provide better outcomes for patients with SA-AKI in the ICU.

By definition, Sepsis is a life-threatening condition of organ dysfunction due to an uncontrolled body's response to a systemic infection. Meanwhile, septic shock is part of sepsis with higher mortality characterized by hypotension requiring vasoactive therapy to maintain an average arterial pressure of at least 65 mmHg and serum lactate above 2 mmol/L despite adequate fluid resuscitation with a mortality rate of>40% [2]. Organ dysfunction caused by inflammatory response can be used to distinguish infections with sepsis, using Sequential Organ Failure Assessment (SOFA) scoring where a minimum of 2 points is the most recent associated with a mortality rate of 10% [3–5]. Critically ill patients with sepsis when patients are undergoing treatment in the Intensive Care Unit (ICU) may experience organ failure, especially in the respiratory system (43%) and the renal system (36%) [6, 7].

2. Literature review

2.1 Definition

According to the latest definition, sepsis is characterized by suspicion or evidence of infection plus clinical signs and laboratory findings that indicate organ dysfunction (based on the SOFA/Sequential Organ Failure Assessment score) due to an immune response to the infection. The heart, liver, lungs and kidneys are organs that are often affected during this process [2]. For a longtime sepsis has been known as a cause of morbidity and mortality; the consensually agreed upon definition of sepsis has only been around for the last few decades [3]. The first consensual definition defined sepsis as a continuous physiological and serological disorder that causes progressive organ failure.

The consensual definition of Sepsis-3 is the response to the limitations of the old definition, where SIRS and severe sepsis are removed. Sepsis is defined as life-threatening organ dysfunction due to the body's uncontrolled response to infection. Organ dysfunction can be identified by a condition of acute changes associated with infection with at least 2 points on a Sequential Organ Failure Assessment (SOFA score), increasing the mortality rate by 10% [2]. The determination of the sepsis diagnosis in patients with infection can use the quick SOFA score, where two of the three criteria can meet the criteria of sepsis. Meanwhile, septic shock is sepsis with hypotension that requires a vasopressor to maintain a minimum MAP of 65 mmHg and serum lactate above 2 mmol/L despite adequate fluid resuscitation; this condition has a mortality rate of 40% [4]. Based on the European Society of Intensive Care Medicine and the Society of Critical Care Medicine's Third International Consensus Definition for Sepsis and Septic Shock in 2016, sepsis is defined as life-threatening organ dysfunction caused by dysregulation of the body's response to infection. So, the criteria for sepsis must also include the three elements, namely, infection, body response and organ dysfunction. The criterion for the diagnosis of sepsis is established through a SOFA (Sequential/Sepsis-related Organ Failure Assessment) score ≥ 2 [5].

Given the significantly high mortality rates, AKI as one of the most frequent complications of sepsis is considered an important issue in clinical practice and especially for hospitalized patients treated in the ICU. This may be due to the limited understanding of the pathogenesis of SA-AKI sepsis, the lack of ability to assess kidney function in early diagnosis of AKI, and the absence of specific treatments other than supportive care [3].

AKI is characterized by a sudden decline in kidney function for several hours to days, resulting in the accumulation of creatinine, urea and other waste products. The latest definition was formulated in the consensus of Kidney Disease: Improving Global Outcome (KDIGO) in 2012, where the AKI was established if it met the criteria: an increase in serum creatinine levels ≥0.3 mg/dL (26.5 μmol/L) within 48 hours, an increase in serum creatinine at least 1.5 times the baseline value within the previous 7 days, or urine volume ≤ 0.5 ml/kg body weight for 6 hours [6].

The initial definition of AKI was the result of the international consensus of the Acute Dialysis Quality Initiative (ADQI) in 2004 that produced RIFLE (Risk, Injury, Failure, Loss, End stage Kidney disease) criteria based on an assessment of increased serum creatinine, decreased Glumerular Filtration Rate (GFR) urine production, loss if AKI lasts >4 weeks and end stage Kidney disease if AKI continues >3 months [7]. Then in 2007, the Acute Kidney Injury Network (AKIN), an international nephrological network or community in the USA and Europe, issued a more specific measure on RIFLE criteria focusing on the condition of the injury, i.e. Risk, Injury, and Failure were changed into stages (stage 1, stage 2, stage 3); Loss and end stage Kidney disease was eliminated; and an increase in serum creatinine of 0.3 mg/dL within 48 hours was added [8].

In 2012, the KDIGO issued clinical guidelines for the management of AKI and made a classification of AKI by combining RIFLE and AKIN criteria. This KDIGO-based classification defines AKI based on an increase in serum creatinine of 0.3 mg/dL within 48 hours or an increase of 1.5 x serum creatinine from baseline or urine production <0.5 ml/kg/hour for 6-12 hours. Baseline serum creatinine is the examination value obtained in the last 7 days. KDIGO also introduced the definition of Acute Kidney Disease (AKD), where an increase in serum creatinine >7 days and < 3 months. This condition occurs due to injury to the kidney and it can also occur slowly, different from AKI with a significant decrease in kidney function occurring within 7 days after the cause of injury to the kidney [9].

In patients who meet both the criteria for sepsis and AKI, it is called SA-AKI [10, 11]. Sepsis can be associated with >50% of AKI cases, and > 60% of sepsis patients can experience AKI. SA-AKI can also be interpreted as AKI which is caused or worsened by sepsis, so that it can be classified as a different condition in AKI which is usually caused by nephrotoxic regimens and ischemic conditions. The inflammatory response is more prominent in SA-AKI compared to nephrotoxic and ischemic AKI [12, 13]. SA-AKI is a clinical syndrome due to acute damage to organ function and damage. It is related to long-term adverse outcomes depending on the severity of the underlying organ damage. In general, SA-AKI should be considered a syndrome, characterized by fulfilling the criteria for sepsis and AKI [6].

2.2 Epidemiology

Acute Kidney Injury (AKI) is a syndrome with a broad spectrum of etiology and various mechanisms; ischemia/hypoxia, nephrotoxics and inflammation play a role in the development of AKI. Among the various etiologies of AKI, sepsis is one of the main causes of AKI in the ICU. According to various reported data, 45-70% of all AKI cases are related to sepsis [8]. Among ICU patients in general, the incidence of AKI varies from 6–67% depending on the study population. The incidence of SA-AKI in patients treated in ICU varies from 13–78% depending on the severity of sepsis and the AKI criteria used. In patients with critical illness with AKI, as many as 20-67% also suffer from sepsis, severe sepsis or sepsis shock. Research conducted by Angus and others on 192,980 patients with severe sepsis from seven states in the United States found that AKI occurred in 22% of sepsis patients with a mortality rate of 38.2%. Whereas in the cohort study conducted by The Sepsis Occuring

in Acutely Ill Patients (SOAP) on 3,147 patients treated in 198 ICUs throughout Europe, 37% of patients had sepsis and AKI occurred in 51% of them with a mortality rate in ICU of 41%. The FINNAKI study of 2,901 critically ill patients treated in ICU in Finland found that among 918 patients with severe sepsis, 53% met the KDIGO criteria for AKI [6].

SA-AKI is associated with a higher risk of death and mortality in hospitals. If the MMR has an overall mortality rate of 45%, the mortality rate of SA-AKI is much higher, which is above 70%. Bagshaw and others in their study found that mortality rates from SA-AKI cases in hospitals and intensive care units/ICUs had increased by 30% and 20% respectively, but it was also suggested that the severity of AKI had a positive correlation with morbidity and mortality rates of ICU patients, the higher the severity of AKI, the higher the mortality rate. Population at high risk for SA-AKI are elderly patients, females, and those with the presence of comorbidities such as diabetes mellitus, chronic kidney failure, congestive heart failure and malignancy. Sources of infection and side effects from treatment also contribute to risk factors for SA-AKI such as intra-abdominal infections, urosepsis, endocarditis and bloodstream infections [14, 15].

2.3 Etiology

Acute Kidney Injury (AKI) is a syndrome with a broad spectrum of etiology. Based on the mechanism of the cause, AKI can be divided into pre-renal, renal, and post-renal AKI.

1. The cause of pre-renal AKI is renal hypoperfusion, due to hypovolemia or a decrease in effective circulation volume, such as in the case of sepsis and heart failure, and intrarenal haemodynamic disorders, such as the use of non-steroidal anti-inflammatory drugs.

2. Renal AKI is caused by abnormalities in the vascular or tubular components of the kidney directly, such as vasculitis, malignant hypertension, acute glomerular nephritis, interstitial nephritis, nephrotoxic substances, etc., causing intrarenal vasoconstriction, ischemia and decreased renal filtration rate.

3. Post renal AKI is usually caused by intrarenal and extra renal obstruction problems that interfere with kidney blood flow [14].

2.4 Pathophysiology

The pathophysiology of the SA-AKI is not yet fully known, and so far it has only been known from the results of studies on animal models that may be of relevance only to specific conditions in humans. From studies in animals and humans, SA-AKI occurs due to an excessive inflammatory response that causes injury to the kidneys, injury to the tubular tight junction, cell cycle arrest, cellular apoptosis and others [4].

The immune response to sepsis will cause microcirculation dysfunction (in tubular and glomerular capillaries) due to the proinflammatory response resulting in injury to endothelial cells. Vascular permiability will increase and there will be a decrease in endothelial Nitric Oxide Synthase (eNOS) activity, which functions to inhibit platelet aggregation and leukocyte activation. Meanwhile, induction of Nitric Oxyde Synthase (iNOS), which works otherwise, will increase its activity. This condition will cause ischemia and hypoxia. Inflammatory reactions will also cause a cycle cell arrest and apoptosis as a form of protection so that the damage is

not widespread. As a result of ischemic and hypoxia, cells will lack energy so that the mitochondria work abnormally, causing injury to the mitochondria, so that injury to the kidneys continues and kidney function will be disrupted.

In sepsis the pathophysiological process of AKI can be caused by the following process:

1. Ischemic vasodilation, causing a decrease in Renal Blood Flow (pre renal AKI) due to an increase in Nitrides Oxyde induced by iNOS.

2. Endothelial leakage, causing edema and increased renal interstitial hydrostatic pressure (glomerulus and tubules), thereby reducing kidney filtration.

3. Nephrosis of the nephron due to the release of neutralizing agents triggered by the release of mediators in sepsis (the formation of ROS or the ischemic process itself causes necrosis of the nephron).

4. Capillary microtrombus due to coagulopathy and platelet leukocyte activation in the kidney endothelium.

2.4.1 Early detection of SA-AKI

Sepsis and AKI can each increase morbidity and mortality, length of stay, and treatment costs, so early detection of SA-AKI is very important to be able to intervene earlier and provide better outcomes for patients. Especially for AKI, given the definition and classification generated from the consensus, it can actually be easier to diagnose AKI by the method of assessing the increase in serum creatinine and urine production. However, this method has limitations, where changes in serum creatinine run slowly and assessment of urine production is usually only routinely done in the ICU. Therefore, several bio-markers have begun to be investigated to be able to detect SA-AKI earlier. Biomarkers can be categorized into two groups: 1. Assessment of renal function, 2. Detection of injury to kidney cells. Biomarkers for detecting SA-AKI include: Cystatin C (Cys-C), Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1), Interleukin-18 (IL-18), Liver Type Fatty Acid -Binding (L-FABP), soluble-triggering receptor Expressed on Myeloid cells-1 (sTREM-1) and Activating Transcriptional Factor-3 (ATF-3). The sensitivity and specificity of the biomarkers varies depending on the time of measurement and the type of sample used. In general, biomarkers from blood (serum) are lower in sensitivity compared to biomarkers from urine samples [16, 17].

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is currently the chosen biomarker in AKI cases, because it can be a biomarker for proximal tubular function and for kidney injury. Below (**Table 1**) are some biomarker studies that assess the time, sensitivity and specificity of several biomarkers derived from serum and urine to detect SA-AKI from the last few years.

2.5 Clinical description

Signs and symptoms of sepsis vary not only with regard to organ involvement, but also from one individual to another because of the patient's special characteristics, vulnerability, and disease. Signs of sepsis reflect the phase of the disease and vary from symptoms confined to the main organ (e.g pneumonia) to severe multi-organ dysfunction syndrome (MODS) and septic shock. Health care workers must be alert for signs of infection, sepsis or septic shock when evaluating patients for kidney failure. Conversely, it is important to frequently monitor kidney

	Time	AUROC	Threshold value	Sensitivity	Specificity	References
Urine Biomarker						
NGAL (ng/mL)	12 hours after septic shock	0.86	>68	0.71	1.0	Martensson et al.
Cys-C (mg/L)	8 hours after patients have been treated	0.86	0.106	0.85	0.80	Aydogdu et al.
NGAL (ng/mL)	7 hours after onset of sepsis	0.86	402	0.89	0.74	Fan et al.
NGAL (ng/mL)	24 hours after patients have been treated	0.78	350	0.75	0.82	Matsa et al.
Serum Biomarker						
NGAL (ng/mL)	12 hours after septic shock	0.67	>120	0.83	0.50	Martensson et al.
Cys-C (mg/L)	8 hours after patients have been treated	0.82	1.5	0.73	0.68	Aydogdu et al.
NGAL (ng/mL)	24 hours after patients have been treated	0.88	400	0.79	0.75	Matsa et al.

From the above mention, it can be shown that both NGAL and Cyst C measurements from urine have higher sensitivity and specificity than serum and both of them can be detected earlier than creatinine. It can be also detected as urine biomarkers. *NGAL: Neutrophil Gelatinase-Associated Lipocalin.*
** Cys-C: Cystatine C.*

Table 1.
Research with NGAL and Cys-C biomarkers.

function (along with other organ involvement) in patients with documented or suspected sepsis.

Clinical studies based on physiological data and some postmortem reports have recently begun to define AKI caused by sepsis and how it differs from other types of kidney injury. Histologically, AKI induced by sepsis is characterized by heterogeneous tubular cell injury with apical vacuolization, but in the absence of tubular necrosis or even extensive apoptosis. All of these features can develop in the context of normal or increased renal blood flow (Renal Blood Flow/RBF) and represent a clinical phenotype characterized by decreased levels of glomerular filtration (GFR), creatininclearance, and uremia [18].

2.6 Diagnosis

A diagnosis of AKI caused by sepsis requires a diagnosis of sepsis and subsequent events of AKI. This is considered a PIRO (predisposition, infection, response, organ dysfunction) system. The diagnosis of sepsis is more complex than the original. In the new definition, several other important aspects of sepsis are included such as hemodynamics and organ dysfunction [18].

A 2016 task force organized by the national community including the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) proposed a new definition of sepsis, called Sepsis-3. This consensus defines sepsis as life-threatening organ dysfunction caused by dysregulation

of the responhost to infection. The new definition does not use the Systemic Inflammatory Response Syndrome's (SIRS) criteria in the identification of sepsis and elimination of severe sepsis [18].

Sequential Organ Failure Assessment (SOFA) is a simple and objective score that allows for calculating both the number and severity of organ dysfunction in six organ systems (breathing, coagulation, liver, cardiovascular, kidney, and neurological), and the score can measure individual or aggregate organ dysfunction [19].

Early detection of AKI in ICU settings is very important. AKI has become a major issue with the increasing number of incidents, causing more than four million deaths per year worldwide. Also, the lack of a reliable initial biomarker for AKI causes a significant delay in starting an appropriate therapy. This is in contrast to the "biological revolution" in cardiology, which produces various markers (including troponin) for early diagnosis of heart damage that allows for early and effective treatments [19].

The diagnosis of AKI is based on an increase in serum creatinine and/or a decrease in urine output. The definition has evolved from the criteria of Risk, Injury, Failure, Loss, Endstage (RIFLE) (**Table 2**) in 2004 to the classification of the Acute Kidney Injury Network (AKIN) in 2007. In 2012, the two were merged, forming the Kidney Disease Improving Global Outcomes (KDIGO) classification [10].

Combined with evidence-based medicine, KDIGO published KDIGO guidelines in March 2012 and established diagnostic criteria for AKI (**Table 3**): increase in serum creatinine >0.3 mg/dl (26.5 μmol/L) within 48 hours; or an increase in serum creatinine to 1.5 times the baseline, which is known or thought to have occurred within 7 days; or urine output <0.5 ml/kg/hour for 6-12 hours. According to the severity, this condition is divided into stages 1, 2, and 3, similar to the classification of AKIN [10].

Categories	Serum Creatinine Criteria	Urine Output Criteria
RIFLE*		
Risk	↑ in SCr to 1.5 – < 2 x baseline	UO <0.5 mL/kg/hr. for 6 hrs
Injury	↑ in SCr to 2 – < 3 x baseline	UO <0.5 mL/kg/hr. for 12 hrs
Failure	↑ in SCr to ≥3 x baseline	UO <0.3 mL/kg/hr. for 24 hrs or Anuria for 12 hrs
Loss	Loss of Kidney function for >4 wks	
ESRD	Loss of Kidney function for >3 mos	
AKIN**		
Stage 1	↑ in SCr to 0.3 mg/dL or to 1.5 – 2 x baseline	UO <0.5 mL/kg/hr. for >8 hrs
Stage 2	↑ in SCr to >2 – 3 x baseline	UO <0.5 mL/kg/hr. for >12 hrs
Stage 3	↑ in SCR to >3 x baseline or	UO <0.5 mL/kg/hr. for >24 hrs
Stage 4	SCr ≥ 4 mg/dL with an acute increase of ≥0.5 mg/dL	or Anuria for 12 hrs

There are little bit differences between RIFLE and AKIN Criteria, LOSS and ESRD in RIFLE criteria are included in Stage 4 in AKIN criteria. *RIFLE: Risk, Injury, Failure, Loss, ESRD (End Stage Renal Disease; AKIN: Acute Kidney Injury Network.*
** *AKIN Criteria require the increase of serum creatinine to occur within 48 hrs; SCr: Serum Creatinine; UO: Urine Output.*

Table 2.
RIFLE and AKIN CRITERIA of AKI.

Stage	Serum Creatinine and urine output criteria
1	Serum creatinine increased 1.5 – 1.9 x baseline or increase ≥26.4 umol/L (0.3 mg/dL) or urinary output <0.5 ml/kg/h during a 6 hour block
2	Serum creatinine increased 2.0 – 2.9 x baseline or urinary output <0.5 ml/kg/h during two 6 blocks
3	Serum creatinine increased >3 x baseline or increased to ≥353 Umol/L (4 mg/dL) or initiation of renal replacement therapy or Urinary output <0.3 ml/kg/h during more than 24 hours or anuria For more than 12 hours

KDIGO: the Kidney Disease Improving Global Outcomes.
KDIGO criteria is most simple than RIFLE and AKIN, there are only 3 stages of AKI, but still using creatinine serum and urine output criteria.

Table 3.
KDIGO criteria of AKI.

The KDIGO guidelines highlight early diagnosis and treatment of AKI and diagnostic markers remain at serum creatinine levels. Because serum creatinine tests are convenient and inexpensive, they can be used as practical clinical indicators. However, there are some limitations. Renal hypoperfusion due to prerenal causes can cause an increase in creatinine, although there is no interference with the renal parenchyma. When the renal parenchyma is injured, renal compensation can cause lag in creatinine increase. Further, injury to 50% of the kidneys can occur without an increase in creatinine levels, so diagnosis and intervention are delayed. Thus, new markers with higher sensitivity and specificity are expected to help the initial diagnosis of AKI. At present, many studies report the presence of early diagnostic markers of AKI. Some of them are clinical trials that show good sensitivity and specificity, with initial diagnostic values for AKI. In addition, different biological markers have been shown to show various mechanisms of injury [20].

Evidently, AKI occurs through complex mechanisms often due to several factors. Different mechanisms cause injury in various parts of the kidney. It is difficult to establish a clear diagnosis and accurate localization of the injury using the same marker to diagnose injury to all kidney subregions caused by all diseases. Discrete studies of certain diseases and related kidney injuries will definitely improve diagnostic accuracy. About 45 – 70% of MMR is associated with sepsis, which is one of the most important causes of MMR. Furthermore, the proportion of septic patients with secondary kidney injury is 16 – 50%, whereas the mortality of sepsis associated with AKI is up to 50 – 60%. As such, pursuing focused studies of sepsis-induced AKI and searching for biomarkers associated with early diagnosis will help in solving important clinical problems of septic patients and AKI disease [20].

2.7 Management

As with sepsis management in general, the main therapy for SA-AKI is the provision of appropriate antibiotics and good supportive care. There are several things that must be considered in the management of SA-AKI:

2.7.1 Fluid therapy

Giving fluids is still fundamental in the treatment of sepsis. Patients who are responsive after being given fluids (fluid responder) can theoretically be interpreted as patients who have increased the stroke volume of 10-15% after giving a fluid challenge of 250-500 ml; in reality, there are less than 40% of sepsis patients who need fluids or fluid responder. Based on the Frank-Starling principle, if

preload increases, the stroke volume will increase until it reaches the optimal preload volume. And if the preload given can no longer increase stroke volume, the volume of liquid given can be dangerous because it can increase arterial pressure, venous pressure, and ultimately pulmonary hydrostatic pressure. Further, the condition will stimulate the release of natriuretic peptide causing fluid transfer from the intravascular space to the interstitial space. Kidney function will also be affected by this condition where there is a decrease in GFR due to increased venous pressure, potentially increasing subcapsular pressure in the kidneys due to fluid transfer.

The "Fluid Expansion as Supportive Therapy" (FEAST) research can explain the dangers of giving fluid loading to patients with sepsis, where aggressive fluid therapy is associated with increased mortality.

In 2001, the concept of "early aggressive fluid resuscitation" was issued, known as the Early Goal Directed Therapy (EGDT). Following this, studies began using the EGDT protocol. It is interesting to find the reduction in mortality by reducing the volume of resuscitation fluid in the first 72 hours. Although the early sepsis phase shows an effective condition of circulating volume reduction, making it possible for fluid resuscitation to take place, the subsequent fluid therapy given can cause problems especially in the SA-AKI [21]. Besides being unable to improve septic shock, fluid therapy can also contribute to causing renal dysfunction through several mechanisms. The most rapid occurrence is an increase in venous pressure due to fluid therapy that directly increases the renal interstitial pressure and peritubular area in animal models [22]. Because the administration of large fluid boluses (20-30 ml/kg) is associated with the occurrence of fluid overload, it is currently recommended to use fluid volumes with lower volumes (200-500 ml) [22]. The 2014 Acute Dialysis Quality Initiative (ADQI) recommends giving fluid therapy to sepsis patients divided into 4 stages, namely using the rescue protocol, optimization, stabilization and de-escalation. A large liquid volume of 500 ml in a maximum of 15 minutes only at the rescue stage is given to overcome hypotension with close monitoring. At the optimization stage, a 100-200 ml fluid challenge for 5-10 minutes can be done. At the stage of stabilization, the patient is stable and fluid administration is a maintenance therapy of 1-2 ml/kg/hour.

The three stages above are followed by de-escalation, which is the stage to reduce total body fluids with the help of diuretics or Renal Replacement Therapy (RRT) with the target of negative cumulative fluid balance. Assessment of volume status during fluid therapy can proceed with the Passive Leg Raising method combined with measurement of stroke volume in real-time. This procedure is proven to be the most precise in assessing volume status clinically. The availability of ultrasound equipment in the ICU can prevent fluid overload by assessing the B-line on the Lung Ultrasound and the vena cava collapsibility index to assess the fluid responder. The MAP target of 65 – 75 mmHg is an adequate target for maintaining renal perfusion [22].

Fluid selection is also a consideration in the SA-AKI. Normal 0.9% saline is actually a non-physiological fluid and is less well administered to SA-AKI than other crystalloids. Normal saline can cause hyperchloremic metabolic acidosis, which can cause a decrease in Renal Blood Flow (RBF) by activating the mechanism of tubuloglumerular feedback and afferent vasoconstriction so as to increase the risk of further kidney injury. In a retrospective study involving 60734 adults with septic shock, normal single saline can increase mortality compared with crystalloid balance solution. Albumin has also been investigated for its use in sepsis patients with the risk of SA-AKI in the SAFE study, showing that albumin was not effective in reducing mortality and RRT requirements when compared with crystalloid fluids [23]. So that until now albumin cannot be recommended as a resuscitation fluid in SA-AKI. Hydroxyethyl Starches (HES) is not recommended and should not be used on SA-AKI.

2.7.2 Vasopressor

Norepinephrine is still the main therapy for septic shock and has been shown to increase MAP and improve perfusion to the kidneys. Norepinephrine itself is the first choice in various clinical studies and provides better outcomes and fewer side effects than other vasopressors. However, due to animal studies showing that norepinephrine can cause medullary hypoxia renal in SA-AKI, researchers have begun to look for other vasopressors in the condition of sepsis and SA-AKI. Vasopressin is the most desirable vasopressor to study; Vasopressin and Septic Shock (VAST) research tries to compare norepinephrine with vasopressin with the same results on the outcome and no side effects are obtained. Further, VANISH research proceeds, the results of which showing the absence of AKI events and side effects of both. Based on these data, vasopressin is the second-line choice of the current vasopressor and has been included in the latest sepsis guidelines. Angiotensin II is a hormone in the renin-angiotensin-aldosterone system which has also begun to be studied in shock conditions. Angiotensin II for the Treatment of High Output Shock (ATHOS) study in 344 patients with shock due to vasodilation (259 with sepsis) found that Angiotensin II significantly increased MAP. Improvements were also seen in SOFA cardiovascular scores. Another smaller study of patients who needed RRT showed that patients who received angiotensin II had a greater 28-day survival rate and were free of RRT on the seventh day more than placebo. If these results can be validated by larger studies, there is a possibility that angiotensin II can be a meaningful therapy for SA-AKI [23].

Levosimendan is a calcium sensitizing drug and has an inotropic effect that is often used in cord decompensation. One small study showed an increase in creatinine clearance and urine production compared to dobutamine. However, in a larger scale study comparing it with placebo (MAKE-28), there was no difference in outcomes in the kidney. So, there is no data to support its use in the SA-AKI [24].

2.7.3 Antibiotics and nephrotoxic substances

The survival rate in sepsis patients will decrease by 7.6% per hour if no appropriate antibiotic therapy is given. Regarding AKI, vancomycin antibiotics are reported to cause AKI even at the recommended dosage for infections caused by methicillin-resistance *Staphylococcus aureus* (MRSA) and it is also reported that vancomycin enhances the nephrotoxic effect of the antibiotic piperazilin-tazobactam. Then other nephrotoxic substances must also be avoided such as Amphotericin B, iodine contras substances, godalinium (a contrast agent for MRI) that can cause AKI [24].

2.7.4 Renal Replacement Therapy (RRT)

There are several aspects that must be considered in kidney replacement therapy, namely indication, time, modality and dosage given. Clinical indications that have been known so far, which are Acidosis, Electrolyte disturbances, Intoxication, O-fluid Overload and Uremia (A-E-I-O-U), can be applied to SA-AKI. Severe metabolic acidosis, fluid overload and uremia are the three most common indications of RRT in SA-AKI [24].

Criteria for Renal Replacement Therapy (hemodialysis) in critically ill patients with AKI include:

- Oligouria: urine output <2000 ml in 12 hours
- Anuria: urine production <50 ml in 12 hours

- Hyperkalemia: potassium levels>6.5 mmol/L
- Severe acidemia (acid poisoning): pH <7.0
- Azotemia: urea levels>30 mmol/L
- Uremic encephalopathy
- Uteric neuropathy/myopathy
- Uremic pericarditis
- Abnormalities of plasma sodium concentration > 155 mmol/L or < 120 mmol/L
- Hypertemia
- Drug poisoning

At the time of the RRT initiation, the available data give different answers. Although undesirable effects have been reported due to the late initiation of the RRT, leading to increased mortality and poor outcomes in the SA-AKI [25]. Up until this, the RRT initiation is still individual. Bouman et al. showed no significant difference in renal outcomes in early and late hemofiltration in patients who were able to survive. There are two large studies, with conflicting conclusions, specifically designed to determine the time of initiation of RRT in the condition of critically ill patients. The ELAIN study comparing early versus late initiation of the RRT shows the benefits of early strategy in reducing mortality. While in the AKIKI study, the results show the opposite, i.e. early strategy gives negative results. In both of these studies there were differences in inclusion criteria; in the ELAIN study, patients were in KDIGO stage 2 with a SOFA score of 15.6-16.0 while in the AKIKI study patients were in KDIGO stage 3 with a SOFA score of 10.8-10.9. Perhaps because of these different inclusion criteria, the opposite results were obtained. But at the moment there is an ongoing study, the STARRT-AKI study (standard vs. accelerated initiation of renal replacement therapy in acute kidney injury) that might reveal the best RRT initiation time. The most appropriate RRT modalities for SA-AKI are also still different. Some studies show the advantages of Continuous Renal Replacement Therapy (CRRT) compared to Intermittent Hemodialysis (IHD) on survival rates and time spent for the kidney function to improve. Although CRRT is superior to IHD based on its fluid removal ability, with a lack of hypotension in patients, it is more expensive than IHD.

The current CRRT dose is sourced from two large studies with sepsis patients but not specific to SA-AKI, which is 20-25 ml/kg/hour. In the condition of the SA-AKI, the dose given is 30–35 ml/kg/hour. Several studies have shown that increasing the CRRT dose does not provide benefits and improve patient survival.

2.7.5 Antimicrobials during CRRT

CRRT significantly influences the pharmacokinetics and pharmacodynamics of most antimicrobial agents. This is not sufficiently anticipated by the currently recommended dosage guidelines. Patients are significantly at risk of receiving lower doses (underdosing), potentially causing treatment failure and increasing resistance.

2.7.6 Diuretics

The use of diuretics to induce or increase urine production in the absence of hypervolemia is associated with increased mortality. KDIGO does not recommend the use of diuretics in the prevention or treatment of AKI. Conversely, diuretics can be used to improve outcomes when fluid balance remains positive or in the case of excess fluid (volume overload). Research by Ho and Power reviewed the use of furosemide in AKI and found no beneficial effect in reducing mortality.

2.8 Prognosis

Compared with other AKI etiologies, SA-AKI may have specific prognostic implications. In most reports, this is associated with higher short-term mortality rates. In the analysis of the BEST Kidney trial subgroup, the likelihood of hospital death is 50% higher in SA-AKI compared to non-SA-AKI. Obviously, the different prognosis between SA-AKI and non-SA-AKI is largely influenced by the composition of the non-sepsis group and its proportion from conditions with a poor prognosis (such as cardiogenic shock). In addition, the confusing role in the relationship between SA-AKI and mortality needs to be overcome because all studies consistently report higher disease severity at onset, with patients requiring RRT more frequently [6].

In contrast, for patients who survive in the hospital, SA-AKI has been associated with improved kidney improvement compared to other etiologies of AKI. In the BEST Kidney study, there was a tendency for lower serum creatinine and RRT dependence (9 vs. 14%, P = 0.052). Clearly, many other factors may play a role in kidney recovery such as RRT modality, RRT time, and further nephrotoxic or ischemic inhibition. Kidney recovery is also strongly influenced by premorbid conditions as illustrated by a French multicentric observational study, which shows that diabetic patients with SA-AKI who have survived going to the hospital tend to need more long-term RRT and have higher serum creatinine levels. Apart from short-term recovery, however, it is now clear that even one episode of AKI is associated with a greater risk of subsequent CKD and even end-stage renal disease [4].

3. Conclusion

SA-AKI is a clinical syndrome due to acute damage to function and organ damage associated with long-term adverse outcomes depending on the severity of the underlying organ damage. Generally clinical manifestations of AKI are more dominated by factors of precipitation or its main disease. The main purpose of managing AKI is to prevent further kidney damage and keep the patient alive until his kidney physiology returns to normal function. SA-AKI is a condition that is often faced by patients with sepsis in the ICU. Understanding of sepsis and endotoxins that can cause SA-AKI is not yet fully known. Some evidence suggests that renal microcirculation hypoperfusion, lack of energy for cells, mitochondrial dysfunction, endothelial injury and cycle cell arrest can cause SA-AKI. Rapid identification of SA-AKI events, antibiotics and appropriate fluid therapy are crucial actions in the management of SA-AKI. The availability of modality for organ support such as CRRT in ICU care can help patients with sepsis, due to kidney failure that often occurs, survive. Further studies related to SA-AKI are still continuing and are expected to be the basis for making a clinical guide in the management of SA-AKI.

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Author details

Titik Setyawati, Ricky Aditya and Tinni Trihartini Maskoen*
Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

*Address all correspondence to: drtitiksetyawati73@gmail.com

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