

Sepsis and Acute Kidney Injury

Beliz Bilgili, Murat Haliloğlu, İsmail Cinel

Department of Anaesthesiology and Reanimation, Marmara University Faculty of Medicine, İstanbul, Turkey

Acute kidney injury (AKI) is a clinical syndrome which is generally defined as an abrupt decline in glomerular filtration rate, causing accumulation of nitrogenous products and rapid development of fluid, electrolyte and acid base disorders. In intensive care unit sepsis and septic shock are leading causes of AKI. Sepsis-induced AKI literally acts as a biologic indicator of clinical deterioration. AKI triggers variety of immune, inflammatory, metabolic and humoral pathways; ultimately leading distant organ dysfunction and increases morbidity and mortality. Serial measurements of creatinine and urine volume do not make it possible to diagnose AKI at early stages. Serum creatinine influenced by age, weight, hydration status and become apparent only when the kidneys have lost 50% of their function. For that reason we need new markers, and many biomarkers in the diagnosis of early AKI activity is assessed. Historically “Risk-Injury-Failure-Loss-Endstage” (RIFLE), “Acute Kidney Injury Network” (AKIN) and “The Kidney Disease/ Improving Global Outcomes” (KDIGO) classification systems are used for diagnosing easily in clinical practice and research and grading disease. Classifications including diagnostic criteria are formed for the identification of AKI. Neutrophil gelatinase associated lipocalin (NGAL), cystatin-C (Cys-C), kidney injury molecule-1 (KIM-1) and also “cell cycle arrest” molecules has been concerned for clinical use. In this review the pathophysiology of AKI, with the relationship of sepsis and the importance of early diagnosis of AKI is evaluated.

Key Words: Acute kidney injury, sepsis, biomarkers, KDIGO, RIFLE

Introduction

Sepsis is a serious clinical picture caused by the systemic response against infection, including organ dysfunction at a certain level (1). Today, sepsis and septic shock account for 37% of the hospitalisations in intensive care units and are the most common causes of death (2). The symptoms and findings of sepsis are non-specific. Leucocyte count, body temperature and presentation of bacterial antigens in plasma and body fluids support the clinical diagnosis. While the gold standard is positivity of blood culture in the presence of clinical findings, the importance of “suspicion” in the diagnosis of possible sepsis has recently been put forward in the concept of early diagnosis and treatment. Acute kidney injury (AKI) is a clinical syndrome displaying itself with a rapid reduction in glomerular filtration rate, accumulation of nitrogenous waste products, such as urea and creatinine, and disorder of acid-base and fluid and electrolyte balances. AKI is seen in approximately 35% of intensive care patients. The most important causes in more than 50% of AKI cases are sepsis and septic shock. The mortality rate of sepsis-associated AKI varies between 20.9% and 56.8%, depending on the intensity of injury (3). It is emphasised that the continuous increase of AKI and sepsis incidence has become an important clinical and public health problem (4, 5). Early diagnosis and good knowledge of the pathogenesis of AKI, which has become such a big problem in intensive care units, are important.

The two-way relationship between sepsis and AKI

The incidence of sepsis and AKI in critical patients is gradually increasing, and both of them indicate a poor prognosis (4). AKI with sepsis increases mortality significantly (6). While being a multifactorial complex syndrome, the most common causes of AKI are sepsis and septic shock (3, 6). In various epidemiologic studies, AKI occurs in 11%-60% of septic patients, depending on definition and the population investigated (3). AKI incidence increases with the severity of sepsis; 19% of sepsis patients, 23% of severe sepsis patients and 51%-64% of septic shock patients are seen with AKI (6-8).

Today, sepsis-associated AKI in the intensive care unit has become a widespread and important problem (3). AKI not only worsens the course of sepsis but also is a predisposing factor in sepsis development (9). For instance, it was seen that sepsis

developed as a complication of renal damage in 45% of patients in whom AKI developed in association with contrast media and who died afterwards (10). A significantly high level of infection occurred in patients in whom AKI developed after cardiovascular surgery compared to those who did not develop AKI (59% against 24%, $p > 0.001$) (11).

Similarly, the incidence of bloodborne infection occurrence in patients developing AKI and requiring renal replacement therapy is higher compared to that of patients having no renal damage (8.8% against 3.5%, $p < 0.001$) (12). However, our knowledge about the role of sepsis in patients developing nonseptic AKI is very limited. In the multi-centric observational study of AKI including 618 patients (The Program to Improve Care in Acute Renal Disease; PICARD), patients who did not develop sepsis, those who developed sepsis after AKI diagnosis and patients having developed sepsis before they were diagnosed with AKI were compared. It was observed that sepsis developed in 40% of the patients with an AKI diagnosis during their hospitalisation and that half of them developed sepsis within 5 days after they were diagnosed with AKI (13). The information above indicates that the sensitivity of AKI patients against infections and sepsis increased (14).

Acute kidney injury affects morbidity, mortality and long-term survival out of the hospital in many clinical conditions (15-17). This is more apparent when sepsis and AKI exist together in clinical patients. It was seen in many observational studies that sepsis-associated AKI differs from nonseptic AKI in terms of demographic and clinical characteristics. It has been detected that patients having sepsis-associated AKI have many accompanying diseases, the acute disease is more serious and physiological changes are more evident compared to those having nonseptic AKI. Sepsis-associated AKI significantly affects the hospitalisation duration, recovery of renal function and mortality rate (3). Moreover, AKI is one of the complications in patients developing mild pneumonia (18).

While there is not much information about the long-term outcomes of discharged patients who developed sepsis-associated AKI, although renal function recovered in most of the patients, it was indicated that the risk of death increased 3.2 times within 2 years. Similarly, in the same study, it was detected that the AKI-associated mortality risk increased in patients with persistent community-acquired pneumonia for a long time after having been discharged from the hospital (18). The mechanism underlying the poor prognosis in the long term after sepsis-associated AKI is not known. However, it was suggested that patients developing sepsis-associated AKI constituted the high-risk group who was unsuccessful in the stress test; therefore, the long-term morbidity and mortality rates were high (19).

After nonseptic AKI, infection and sepsis in the following period generally develop as complications (9). Levy et al. (10) identified sepsis as the most important factor to affect total

mortality in the patient population developing AKI after contrast material and mortality following it. For sepsis development after AKI, oliguria lasting ≥ 3 days, fluid overload at the time of diagnosis, non-surgical invasive procedures and serious disease and dialysis requirement were counted among the risk factors. The concept of "renal angina" has recently been defined in this context, and fluid overload, having been involved in the diagnostic criteria, was emphasised to be a predictor of renal angina before AKI.

After the demonstration of fluid overload lowering the survival rate in intensive care units, the importance of the role of fluid overload in AKI development and renal angina was supported by an increasing number of studies (20-22). In-hospital mortality rate was significantly higher in patients developing sepsis after acute kidney injury compared to patients not developing sepsis ($p < 0.001$) and similar to those developing acute kidney injury after sepsis. Hospitalisation duration of patients developing sepsis after AKI was extended compared to patients not developing sepsis, and the rate of receiving dialysis increased. Consequently, AKI plays an important role in an organisms' response and the development of septic complications (13).

AKI mostly develops as part of multiple-organ failure syndrome in sepsis and the early period of septic shock (8). The nephrons' highly organised structure brings about a different response, although it shares the pathophysiological mechanisms responsible for the dysfunction of other organs. Additionally, new proof has shown that sepsis-associated AKI and nonseptic AKI have different pathogenic mechanisms (23).

Sepsis-associated AKI progresses highly oliguric in spite of fluid treatment (3). As a result of this, nosocomial infections and sepsis risk increase, wound healing delays, organ dysfunction develops (aggravated by interstitial oedema) and organ function returning to normal is delayed (13, 14, 24). Besides, the toxic impacts of organic wastes, like uremic toxins, contribute to the high morbidity and mortality of sepsis by causing oxidative stress, inflammation and insulin resistance (25). On the other hand, empirical studies carried out have demonstrated that not only uraemia but also renal failure play a critical role in distant organ dysfunction (26).

It is suggested that the negative effect of acute kidney injury on mortality in sepsis depends on the side effects of renal replacement treatment. In the "EPISEPSIS" study, it was demonstrated that renal replacement therapy is correlated with increased mortality (27). Although there is no exact information about this, the inflammatory response caused by dialysis, reduction of antioxidants and infection related with the dialysis access site are accused of it (28).

Pathogenesis of sepsis-associated AKI

Since the mortality rate in sepsis-associated AKI is very high, fast diagnosis and initiation of appropriate treatment are necessary. However, contradictory information about sepsis-as-

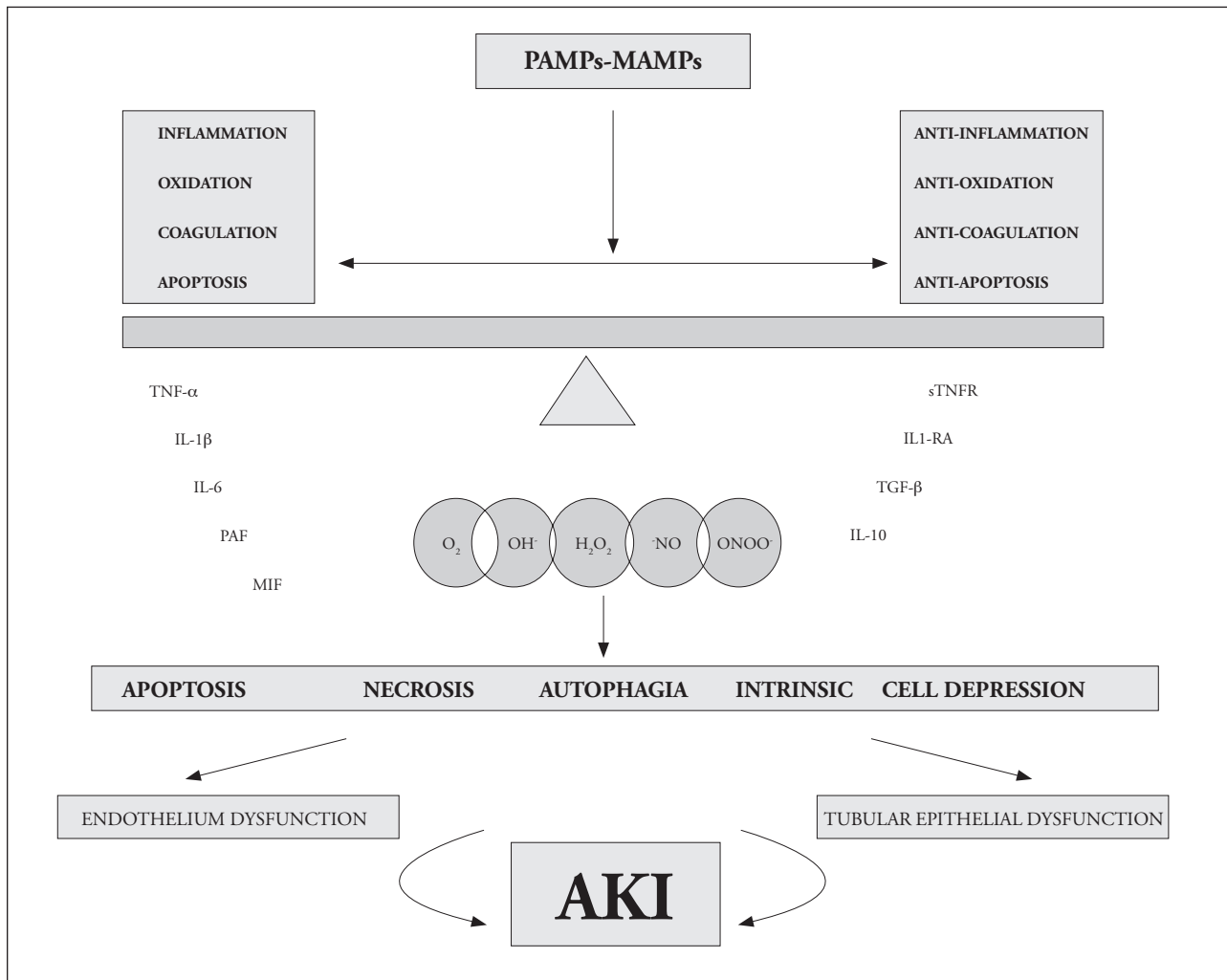


Figure 1. Key pathogenic pathways in sepsis and sepsis-associated-AKI pathophysiology
 PAMPs: pathogen-associated molecular patterns; MAMPs: microbe-associated molecular patterns; TNF: tumour necrosis factor; IL: interleukin; PAF: protease-activating factor; MIF: migration inhibitory factor; HMGB: high-mobility group box; sTNFR: soluble necrosis factor receptor; AKI: acute kidney injury

sociated AKI and not being able to provide a general consensus delay the diagnosis and treatment initiation (8, 29). The pathophysiology of AKI during sepsis is complex and multifactorial and involves changes of renal haemodynamics, endothelial dysfunction, renal parenchymal inflammatory cell infiltration, intraglomerular thrombosis and congestion of tubules by waste and necrotic cells (30). The sepsis-associated immune response involves ordered activation of pro- and anti-inflammatory mechanisms (Figure 1) (31, 32).

After the first interaction of the host and microorganism, a broad-based immune response, including humoral and cellular components, is formed (33). It causes the release of many cytokines, such as IL-1, TNF- α and IL-6; then, the process proceeds with a cytokine storm, haemodynamic instability, organ dysfunction and septic shock (34-36). A compensatory anti-inflammatory phase follows this proinflammatory phase. These two phases may intertwine for a short time (37). Many proinflammatory cytokines contribute to the development of sepsis; for instance, the response formed by recombinant IL-1 and TNF- α application is similar to the response

formed when met with lipopolysaccharide or the response in sepsis (34, 35). Although the beneficial effects of anti-TNF- α monoclonal antibodies were seen in animal sepsis models, no beneficial effects of these or other cytokines were detected (38, 39). In the recent preclinical studies performed, it was suggested that thrombomodulin had an anti-inflammatory role in AKI, and the release of stem cell factor by MMP-9 has antiapoptotic effects with cKit activation (39, 40). Toll-like receptors (TLRs) are kinds of pattern recognition receptors, and they play the role of defence barrier in the first step of the innate immune system. TRL has a role in kidney injury. There are components in pathogens that are not found in the host called pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs). Not only immune cells but also endothelial cells during infection recognise pathogen-associated molecular patterns by TLRs. TLR-4 plays a key role in AKI (41). A significant increase is seen in monocytic TLR-4 and TLR-2 expression of sepsis patients when compared with healthy people. It has been seen that there is an important rise of TLR-4 and TLR-2 expira-

tion in hepatic and splenic macrophages in an experimental peritonitis model conducted with rats (42). These findings demonstrate that TLR modulation can be an important new objective for organ injury treatment in sepsis. Sepsis, at the same time, affects many systems, such as the complement cascade, activation of the coagulation system and venous injury. Consequently, the complex structure of sepsis explains the failure of modalities targeting just one of the many systems affecting it for treatment.

Renal blood flow during sepsis

One of the most controversial issues about sepsis-associated AKI pathophysiology is how renal blood flow changes. It was considered that AKI in hypodynamic shock formed as a result of extended hypoperfusion and renal ischaemia. However, in some animal studies, it was shown that renal and medullary blood flow increased in severe sepsis and sepsis shock. Brenner et al. (43) placed a thermodilution renal blood flow catheter in eight patients with a diagnosis of AKI in the intensive care unit and demonstrated that sepsis-associated AKI may occur in spite of normal renal blood flow. It was stated in a review carried out on experimental AKI models that the most important determinant of renal blood flow was cardiac output. While renal blood flow increases or is protected in sepsis with high cardiac output, it decreases in sepsis with low cardiac output. It was demonstrated in experimental gram-negative bacteraemia and a sepsis model formed by *E. coli* infusion in female merino sheep that renal blood flow increased and vascular resistance decreased. In this hyperdynamic sepsis model, the glomerular filtration rate apparently reduced, serum creatinine increased 4 times and creatinine clearance decreased (44). Similar results were obtained in the sepsis model conducted previously with swine, and an increase of global renal blood flow and medullary blood flow was observed (45). These observations give rise to the thought that renal vascular activity is important in the loss of glomerular filtration pressure. Sepsis-associated AKI is considered to be a hyperaemic kidney injury. The suggested mechanism is the fall of pressure inside the glomerulus due to greater dilation of efferent arterioles compared to afferent arterioles despite the apparent rise of renal blood flow (46). However, in the sepsis-associated AKI picture of humans, to what extent this mechanism is valid has not become definite yet.

AKI diagnosis according to KDIGO guidelines

Rapidly developing renal failure has been marked with various names in history. First, William Heberden in 1802 called this case "ischuria renalis" and "war nephritis" in the 1st. world war years, and finally, Homer Smith in 1951 used the term "acute kidney failure". Currently, this term has also lost its validity, and recently, the term AKI has begun to be adopted, for the last phase of acute renal dysfunction is acute renal failure. Failure term can not describe the early phases of injury. Nowadays, it is not known in whom, when, in what way and how severe the symptoms and complications regarding failure will occur. That is, without the development of the

state of severe failure, kidney injury may lead to life-threatening complications (46). AKI is a definition covering acute renal failure, as well. For instance, while this process probably takes 4-5 hours for a geriatric patient having heart failure and diabetes, it may take longer for a young patient without any additional problems. A young organism may be more resistant to complications. It must not be forgotten that the term AKI may change, as well, following better enlightenment of the process. The early detection of kidney injury is probably more important than its definition. Therefore, it must be concentrated on the detection of injury in the early stage; the necessary actions have to be taken if it is not progressing, and if it progresses, the complications have to be prevented before they pose any danger. Clinical applications and research have been developed to diagnose AKI as a single and simple definition for public health, based on the criteria of "The Kidney Disease/Improving Global Outcomes" (KDIGO), RIFLE (Risk, Injury, Failure, Loss, End Stage-Risk) and AKIN (Acute Kidney Injury Network) (Figure 2). Basal serum creatinine level and the amount of urine are used for this classification. Similar to the AKIN criteria, AKI is separated into three phases. The existence of any of the criteria below is defined as AKI (Table 1):

- A rise of ≥ 0.3 mg dL⁻¹ in the level of serum creatinine level in 48 hours
- A ≥ 1.5 times rise (ungraded) in the level of serum creatinine level, the occurrence of which is known or estimated to be within the last 7 days
- Urine output is 6 hours < 0.5 mL kg⁻¹ (ungraded) (47).

New biomarkers of AKI

Patients have an asymptomatic course up to the advanced stages of the disease, and not being able to diagnose the disease in the early stages by traditional diagnosis methods is one of the reasons of the failure of treatment (48). Although atrial natriuretic peptide was effective for AKI treatment in experimental animal studies, no beneficial effect of it could be shown in clinical studies. Despite all efforts of researchers in clinical studies, not being able to be diagnose AKI early (average creatinine value of the patients involved in the study was 4.5 mg dL⁻¹) is thought to be effective for the results (49). Creatinine is used for the evaluation of renal failure changes with the patient's age, gender and muscle mass. Additionally, it may not rise without an almost 50% decrease of renal function. Therefore, it was studied on tests to provide a diagnosis of AKI in the earlier stages. The most promising ones among them were serum neutrophil gelatinase-associated lipocalin (NGAL) and cystatin-C (Cys-C). The enzymes released from damaged tubular cells are measured in urine. These are proteins that are AKI-associated and synthesised especially from the kidney, cysteine-rich protein 61, kidney injury molecule-1 (KIM-1), liver binding protein (L-FAP), cytokines, chemokines (Gro- α , IL-18) and renal tubular structural and functional proteins (F-actin, Na⁺/H⁺ change isoform 3). By

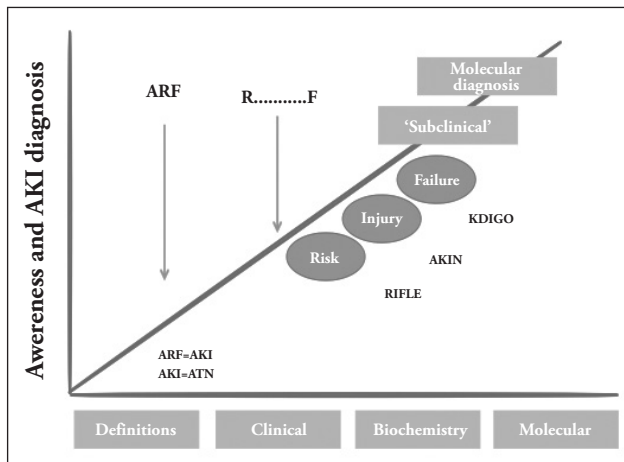


Figure 2. AKI diagnosis

ARF: acute renal failure; AKI: acute kidney injury; ATN: acute tubular necrosis; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease/Improving Global Outcomes-; RIFLE: risk, injury, failure, loss, end-stage

using these markers in serum and urine, the reason for kidney injury, duration, severity and the response of it to the treatment may be estimated.

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein with 178 amino acids, having a weight of 25 kDa, and is synthesised in neutrophils and epithelial cells involving also the proximal convoluted tubule. Since NGAL is detected both in serum and urine after the development of AKI within a short time, such as 2 hours, it is called troponin of the kidney. While serum creatinine begins to rise within 24-48 hours in cardiopulmonary bypass, contrast nephropathy and sepsis-associated AKI, NGAL levels in serum and urine begin to rise within 2 hours (50, 51).

Cystatin-C is a 13.3-kDa and 120-aa nonglycosylated protein that can be synthesised in all nuclear cells and mixes the blood at a constant rate. The serum concentration is not affected by age, gender, race, body mass index and hydration state. However cystatin-C level is affected by thyroid dysfunction, malignancies, inflammation and steroid treatment (52). It is completely reabsorbed from the proximal tubule and catabolised, is not secreted and is measured in serum and urine. In a study conducted in intensive care units, for patients included in the risk group according to RIFLE classification, AKI was detected 1.5 days earlier through serum cystatin-C level than through serum creatinine level. In a study evaluating glomerular filtration rate depending on creatinine clearance in 24 hours, it was detected that cystatin levels correlated with creatinine clearance (54).

Kidney injury molecule-1 is a tubular-based transmembrane protein. It was demonstrated in animal experiments that there was an apparent increase in proximal tubular epithelial cells where damage and restructuring of KIM-1 mRNA was seen, in response to ischemic and toxic AKI (55). When the clinical usability of KIM-1 for the diagnosis and prognosis of AKI was evaluated, a significant increase in KIM-1 levels

Table 1. AKI phases according to KDIGO guideline

Stage	Serum creatinine level	Urine volume
1	1.5-1.9 times or ≥ 0.3 mg dL ⁻¹ increase of basal value	6-12 hours < 0.5 mL kg ⁻¹ hour ⁻¹
2	2-2.9-fold increase of basal value	≥ 12 hours < 0.5 mL kg ⁻¹ hour ⁻¹
3	3-fold increase of basal value or Serum creatinine > 4.0 mg dL ⁻¹ or RRT initiation or $< A$ decrease of < 35 mL dk ⁻¹ 1.73 m ² in GFR of 18-year-old patients	≥ 24 hours < 0.3 mL kg ⁻¹ hour ⁻¹ or ≥ 12 hours anuria

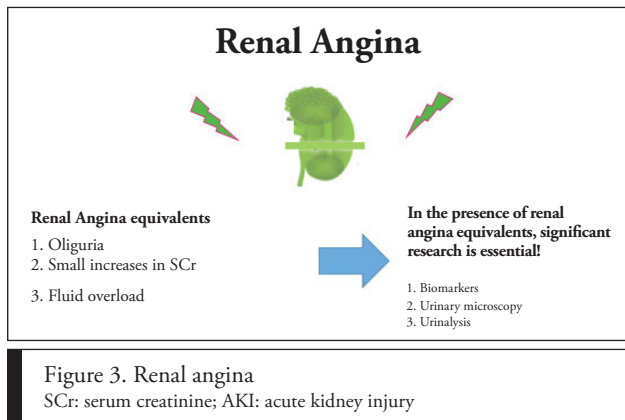
KDIGO: Kidney Disease/Improving Global Outcomes; AKI: acute kidney injury

was observed in patients developing AKI 2 hours after cardiac operations compared to those not developing AKI. In predicting AKI, the sensitivity of KIM-1 was found to be in the range of 92%-100% within 24 hours after the cardiac operation (56).

Interleukin-18 (IL-18), a proinflammatory cytokine, is a marker of inflammation and ischemic tissue damage. In experimental studies, it was indicated that caspase-1-mediated IL-18 activation was effective in AKI formation (55). Its release from the proximal convoluted tubule following AKI increases, and it is detected in urine. It was shown that urinary IL-18 levels rose in 4-6 hours after cardiac surgery and peaked in 12 hours (57). It is thought that urinary IL-18 levels are more specific for ischemic AKI and not affected by chronic kidney injury, urinary tract infection or nephrotoxic damage (58). L-FABP is a small cytoplasmic protein, 14 kDa in weight, and carrying free fatty acids inside the cell. It is synthesised in the proximal tubule of the kidney. In experimental animal studies, it was detected that L-FABP levels reflected the degree of tubulo-interstitial damage (59). Their levels at the 4th hour after surgery of paediatric patients who had undergone coronary bypass operation were evaluated as risk markers of AKI (60).

The main problem here is what will make us think of AKI and direct us to biomarker tests. Goldstein and Chawla (20) recommend renal angina syndrome to overcome this dilemma, and they suggest additionally that biomarkers with renal angina syndrome will increase the sensitivity and specificity of the diagnosis of AKI. According to the authors, there are also risk factors for AKI, like coronary artery disease, and they state that they are 65 age, diabetes, liver failure, congestive heart failure, chronic renal failure and cardiopulmonary bypass. It was emphasised that clinicians had to be careful about kidney angina in patients having risk factors for AKI. Goldstein and Chawla evaluated oliguria, small increases in serum creatinine level and excessive fluid overload as renal angina symptoms (Figure 3).

Acute kidney injury affects many cellular and molecular pathways, including inflammatory, interstitial, endothelial



and epithelial cells. These mechanisms include immunity, inflammation, apoptosis and cell cycle pathways. Renal tubular cells enter into G1 cell cycle arrest stage in the presence of ischaemia or sepsis (61). G1 cell cycle arrest prevents division of the cell with damaged DNA, until it is repaired. Cell cycle arrest takes place right after the damage in the early stage. Insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) are associated with cell cycle arrest in the early stage of cell damage (62).

In a multicentre study in which the strengths of IGFBP7 and TIMP-2 in predicting AKI were evaluated, IGFBP7 and TIMP-2 in urine were measured in intensive care hospitalisation, and AKI (KDIGO phase 2-3) existence was evaluated 12 hours after sampling. Urinary IGFBP7 and TIMP-2 showed better performance than all of the biomarkers defined previously (63). In a study in which urinary IGFBP7 and TIMP-2 performance in predicting AKI development and renal recovery was evaluated, they were shown to be biomarkers having high sensitivity and specificity for both AKI development and renal recovery (Table 2) (64). In a multicentre study in which the strengths of urinary IGFBP7 and TIMP-2 in predicting moderate-severe AKI were evaluated, it was found that values of IGFBP7 and TIMP-2 being above 0.3 increased the risk of AKI 5 times, and their being above 2.0 increased the risk 17 times (65).

Conclusion

Although the most common reason for AKI in critical patients is sepsis, we have limited information about sepsis-associated AKI. Many of the drugs that have been successful in animals for AKI treatment in intensive studies for years are not effective in humans. The fact that sepsis and sepsis shock are the most common reasons for death in intensive care units is an indicator of the requirement for new approaches in the diagnosis and treatment of sepsis-associated AKI. The effectiveness of new biomarkers on the early diagnosis of sepsis-associated AKI has to be tested.

Peer-review: Externally peer-reviewed.

Table 2. AKI biomarkers

Biomarker	Place of sample taken	Rising time in sepsis-associated AKI
IGFBP-7	Urine	Very early
TIMP-2	Urine	Very early
NGAL	Plasma	Early
L-FABP	Urine	Early
Cystatin-C	Plasma	Moderate
KIM-1	Urine	Moderate
IL-8	Urine	Moderate

IGFBP-7: insulin-like growth factor binding protein; TIMP-2: tissue inhibitor of metalloproteinases-2; NGAL: neutrophil gelatinase-associated lipocalin; L-FABP: L-type fatty acid-binding protein; KIM-1: kidney injury molecule-1; AKI: acute kidney injury

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