Chapter 2

Acute Kidney Injury

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Additional information is available at the end of the chapter

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Abstract

Acute kidney injury (AKI), previously named acute renal failure, is characterized by abrupt deterioration in renal function. The incidence of AKI has increased lately, both in the hospital and community setting. It is estimated that more than 13 million people are affected by AKI annually worldwide. Despite all the advances in the field, AKI still carries a high mortality rate. In addition to mortality, AKI is an important risk factor for the development of chronic kidney disease. In this chapter, various aspects of AKI will be discussed including definition and staging, etiology, pathophysiology, clinical presentation, diagnosis, management, prognosis, and prevention.

Keywords: acute kidney injury, renal failure, nephrotoxicity, pathophysiology, biomarkers, management, prognosis, prevention

1. Introduction

Acute kidney injury (AKI) is a major public health concern and is associated with high morbidity, mortality, and healthcare costs. The incidence of AKI has increased lately, both in the hospital and community setting. It is estimated that more than 13 million people are affected by AKI annually with an incidence of 21.6% in adults and 33.7% in children during a single hospital episode of care [1, 2]. Despite all the advances in the field, the mortality of AKI remains very high estimated at 23.9% in adults and 13.8% in children [2]. In addition to the high mortality (1.7 million per year), AKI is associated with high morbidity and high costs [1]. In the United States, at least $5 billion in hospital costs are related to AKI, while in England AKI consumes 1% of the National Health Service budget [3]. In the developed world, AKI manifests mainly in older patients and in the intensive care settings; while in the developing countries, adults and women are particularly more commonly affected [4, 5]. Recovery from AKI is not always, as previously thought, complete and many patients progress to develop

chronic kidney disease (CKD), end-stage renal disease (ESRD), or worsening of preexisting CKD later on in life [6–9]. Treatment of AKI is needed to reduce the high morbidity and mortality and improve recovery of renal function. A part of dialysis, there are no other interventions that reliably improve survival, limit injury, or enhance recovery. The multifactorial etiology and the heterogeneous patient population coupled with the complicated clinical course of patients with AKI has created challenges in the search for effective pharmacological therapy [10]. In some scenarios, such as surgery or administration of intravenous contrast, the onset of AKI can be predicted providing a window of opportunity for intervention and prevention. In the majority of cases, however, intervention takes place after the onset of AKI with the aim to shorten the course and enhance recovery of renal function. In this chapter, various aspects of AKI will be discussed with a particular focus on definition and staging, etiology, pathophysiology, clinical presentation, diagnosis, management, prognosis, and prevention.

2. Definition and staging of acute kidney injury

The term AKI has replaced old terms such as acute renal failure and acute renal insufficiency, which previously had been used to describe the same clinical condition. AKI is not just failure; it also incorporates the entire spectrum of the syndrome, from minor changes in renal function to the most severe form, where renal replacement therapy (RRT) may be required.

Over the last few decades, more than 35 different definitions have been used to define AKI [11]. The most commonly used definition is based on urine output and/or serum creatinine criteria. The most commonly used classifications of AKI are the "risk, injury, failure, loss of kidney function, and end-stage kidney disease" (RIFLE) [12] and the Acute Kidney Injury Network (AKIN) classifications [13].

The RIFLE classification is based on serum creatinine and urine output determinants, and considers three severity classes of AKI (risk, injury and failure), according to the variations in serum creatinine and or urine output, and two outcome classes (loss of kidney function and end-stage kidney disease). The patient should be classified using the criteria which leads to the

Class	GFR	Urine output
Risk	↑ SCr × 1.5 or ↓ GFR >25%	<0.5 mL/kg/h × 6 h
Injury	↑ SCr × 2 or ↓ GFR >50%	<0.5 mL/kg/h × 12 h
Failure	↑ SCr × 3 or ↓ GFR >75% or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑ SCr >44.2 μmol/L (>0.5 mg/dL)	<0.3 mL/kg/h × 24 h or anuria × 12 h
Loss of kidney function	Complete loss of kidney function >4 weeks	
End-stage kidney disease	Complete loss of kidney function >3 months	

GFR, glomerular filtration rate; SCr, serum creatinine.

Table 1. Risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) classification of acute kidney injury [12].

worst classification (maximum RIFLE), **Table 1**. On the other hand, AKI is classified/staged by the AKIN into three stages as shown in **Table 2**.

The Kidney Disease Improving Global Outcomes (KDIGO) work group has combined the RIFLE and AKIN classifications in order to establish one classification of AKI for practice, research and public health. Therefore, AKI is now defined as an abrupt reduction in renal function (within 48 h) based on an increase in serum creatinine level of more than or equal to 0.3 mg/dL (≥26.4 μmol/L), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/h for more than 6 h) or a combination of these factors [14].

Stage	Change in serum creatinine	Urine output
1	Increase ≥0.3 mg/dL (26.52 μmol/L) or ≥150–200% from baseline	<0.5 mL/kg/h for more than 6 h
2	Increase >200–300% from baseline	<0.5 mL/kg/h for more than 12 h
3	Increase >300% from baseline or ≥4.0 mg/dL (353.60 μmol/L) with an acute rise of at least 0.5 mg/dL (44.20 μmol/L)	<0.3 mL/kg/h for 24 h or anuria for 12 h

Table 2. Acute Kidney Injury Network (AKIN) classifications of acute kidney injury [13].

3. Etiology of acute kidney injury

The etiology of AKI can be divided into three categories, **Table 3** [15]:

1. Prerenal (caused by decreased renal perfusion, often due to volume depletion)
2. Intrinsic renal (caused by a process within the kidneys)
3. Postrenal (caused by a process distal to the kidneys such as obstruction)

Prerenal

Intrarenal vasoconstriction (hemodynamically mediated):

Medications: nonsteroidal anti-inflammatory drugs, angiotensin system blockers, calcineurin inhibitors

Cardiorenal syndrome: advanced heart failure

Hepatorenal syndrome: liver cirrhosis

Abdominal compartment syndrome

Hypercalcemia

Systemic vasodilation: sepsis

Volume depletion:

Renal loss: diuretics, osmotic diuresis (severe hyperglycemia), salt wasting

Extrarenal loss: blood loss, gastrointestinal loss (vomiting, diarrhea), skin (burns, sweating)

Intrinsic renal

Glomerulonephritis (isolated or a part of systemic diseases)

Interstitial nephritis:

Medications: antibiotics (β lactams, sulfonamides, quinolones, rifampin), phenytoin, antiretrovirals, proton pump inhibitors, nonsteroidal anti-inflammatory drugs

Infections: viruses (Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus), bacteria (tuberculosis, legionella species), fungi (candidiasis, histoplasmosis)

Systemic disease: sarcoidosis, connective tissue diseases

Tubular necrosis:

Ischemic: prolonged hypotension

Nephrotoxic: exogenous toxins (radiographic contrast agents, aminoglycosides, cisplatin, methotrexate, amphotericin B)

Endogenous toxins: pigment induced (hemolysis and rhabdomyolysis), tumor lysis syndrome, multiple myeloma

Vascular

Renal artery and vein thrombosis, malignant hypertension, scleroderma renal crisis, atheroembolic disease, microangiopathies

Post renal

Extrarenal obstruction: outlet obstruction (prostate hypertrophy, neurogenic bladder; malignancy of the urogenital tract), retroperitoneal fibrosis

Intrarenal obstruction: stones, crystals (acyclovir, indinavir, ethylene glycol), blood clots, tumors

Adapted and modified from Rahman et al. [15].

Table 3. Etiology of acute kidney injury.

Of these three categories, only "intrinsic" AKI represents a true kidney disease, while pre- and postrenal AKI are the consequence of extrarenal processes that lead to decreased glomerular filtration rate (GFR). Both pre- and postrenal conditions, if persist and not managed in a timely manner, may eventually evolve into intrinsic renal damage. Patients with CKD and those admitted to the intensive care unit (ICU) are particularly prone to develop AKI. The AKI-EPI study demonstrated that AKI occurred in more than half of the patients in ICU; mostly due to sepsis and hypovolemia followed by nephrotoxic agents [16].

4. Pathophysiology of acute kidney injury

Despite the identification of several cellular mechanisms thought to underlie the development of AKI, the pathophysiology of AKI is still poorly understood. Animal models of AKI representing ischemia–reperfusion injury and drug nephrotoxicity have been instrumental in understanding the pathophysiology of AKI in humans. Although the current *in vivo* models of AKI in healthy rodents provide valuable information about the pathophysiological mechanisms of renal injury, they do not reflect the complexity of disease in humans characterized by

population's heterogeneity and preexisting comorbidities such as diabetes, hypertension, and CKD. A few and not all mechanisms of AKI will be discussed.

4.1. Microvascular injury

The renal microvasculature plays a key role in the pathophysiology of AKI. The kidney is a vascular organ receiving 25% of the cardiac output and has a high energy demand with relatively low oxygen (O_2) extraction. Under normal steady-state, the O_2 supply to the kidney is well regulated. Adequate O_2 delivery is crucial for the production of mitochondrial adenosine triphosphate (ATP), nitric oxide (NO), and reactive oxygen species (ROS) necessary for homeostatic control of renal function [10, 17]. The vascular architecture of the outer medulla is particularly susceptible to ischemic injury due to the marginal oxygenation of this part of the kidney.

With injury, the microcirculation is compromised leading to an imbalance in NO, ROS, and O_2 supply and consumption. Subsequent pathogenic events follow including hypoxia and oxidative stress. Injury to the microvascular endothelium and changes in the glycocalyx lead to endothelial cell activation and expression of cell surface markers that promote recruitment and adhesion of leukocytes and platelets, leading to further changes in perfusion and O_2 delivery; and to additional endothelial cell injury and inflammation [18, 19]. As a result, increased vascular permeability and development of interstitial edema lead to further compromise of blood flow exacerbating the initial insult. In addition, production of vasoactive prostaglandins by damaged tubular cells coupled with oxidative stress further impairs O_2 delivery by worsening the local microvascular occlusion [18, 19]. The main long-term result of microvascular injury is a reduction in peritubular capillary density, a response to decreased vascular endothelial growth factor (VEGF) and increased transforming growth factor beta (TGF-β) signaling, which contributes to ongoing hypoxia and development of renal fibrosis [20].

4.2. Changes in endoplasmic reticulum

The endoplasmic reticulum (ER) plays an important role in the maintenance of protein homeostasis through its control of the concentration, conformation, folding, and trafficking of client proteins. As a result of endothelial or epithelial cell stress, unfolded or misfolded proteins accumulate in the ER, triggering the unfolded protein response (UPR) [21]. The UPR initially serves as an adaptive response, but will also induce apoptosis in cells under severe or prolonged ER stress. Accumulating evidence indicates that apoptosis in tubules resulting from epithelial cell damage is caused, at least in part, by the proapoptotic UPR [22]. Therefore, targeting the UPR may present a possible approach to prevent or treat AKI.

4.3. Mitochondrial dysfunction

The ER and mitochondria have multiple contact sites termed the mitochondrial-ER-associated membrane (MAM). The MAM contains proteins from the two organelles and appears as ER tubules closely apposed to the mitochondria on electron micrographs [23]. During cellular stress situations, like an altered cellular redox state, the MAM alters its set of regulatory proteins and thus alters MAM functions. In the pathogenesis of AKI, proximal tubules are

especially vulnerable to mitochondrial dysfunction as they depend on aerobic metabolism and their mitochondria are in a more oxidized state than those in the distal tubular cells which can use glycolysis [24]. Following either ATP depletion or cisplatin treatment of rat renal tubular cells, mitochondrial fragmentation was observed prior to cytochrome c release and apoptosis [25]. Targeting mitochondrial dysfunction along with a better understanding of the regulation of mitochondrial dynamics and its pathogenic changes may emerge as a new modality to treat AKI [26].

4.4. Autophagy

Autophagy is a catabolic process in which proteins, organelles, and cytoplasmic components are delivered to lysosomes for degradation and recycling. Autophagy is induced in renal tubular cells during AKI [27]. It is initiated by encapsulating cytoplasmic proteins and organelles in autophagosomes, which fuse with lysosomes for degradation. Once activated, it may decrease cellular stress by removing ER membranes containing UPR sensors and/or clearing abnormal proteins from the ER. In animal models, blocking the autophagic flux-enhanced AKI, while activation of autophagy was found to be protective against cisplatin-induced AKI [27]. In addition, resolution of autophagy may promote proliferation and regeneration of tubular cells in the recovery phase of AKI [28]. Autophagy may be targeted as an inflammatory modulator for the treatment of various kidney diseases [29].

4.5. Inflammation

Inflammation plays a major role in the pathophysiology of AKI resulting from ischemia [30]. Changes in protein folding and mitochondrial function influence the innate immune response, contributing to inflammation. In addition, several cytokines and inflammatory pathways are activated in AKI [30]. Moreover, immune cells of both the innate and adaptive immune systems, such as neutrophils, dendritic cells, macrophages, and lymphocytes, contribute to the pathogenesis of renal injury after ischemia–reperfusion injury, and some cells also participate in the repair process [31]. Neutrophils and monocytes mediate the acute phase within the first 24 h of injury [32], whereas T and B lymphocytes are important in the evolution phase of renal injury [31]. Inhibition of leukocyte infiltration into the kidney ameliorates the loss in renal function, decreases renal injury, cell death, and long-term fibrosis [33]. There is experimental evidence that inducible nitric oxide synthase (iNOS) may contribute to tubular injury during AKI [34]. It has been shown that hypoxia in isolated proximal tubules increases nitric oxide release [35], and that iNOS protein expression is increased in ischemic kidneys [36]. *In vivo* use of an antisense oligonucleotide to block the up-regulation of iNOS was protective against ischemia induced renal injury in rat models [36]. Similarly, tubules from iNOS knockout mice were protected against hypoxic injury [37].

Phospholipase A2 (PLA2) is a family of enzymes that hydrolyzes the acyl group from the sn-2 position of phospholipids, generating free fatty acids [38, 39]. PLA2 activity is increased during hypoxic injury to the renal tubules. Inhibiting PLA2 by exogenous fatty acids such as arachidonic acid has been shown to be protective against hypoxia-induced injury in isolated proximal renal tubules [40, 41].

4.6. Sepsis and acute kidney injury

Sepsis is a severe inflammatory response to infection characterized by a whole-body inflammatory state with severe consequences, including multiple organ failure [42]. AKI is a frequent and serious complication of sepsis among ICU patients and is associated with a high in-hospital and long-term mortality [43, 44]. The multinational AKI-EPI study has demonstrated that AKI affected more than 50% of ICU patients, and increasing AKI severity was associated with increased mortality [16].

4.6.1. Pathogenesis of sepsis-induced acute kidney injury

Although septic shock is a leading cause of AKI, the underlying mechanisms are not completely understood. The pathophysiology of AKI in sepsis is complex and multifactorial involving multiple processes including intrarenal hemodynamic perturbations, endothelial dysfunction, infiltration of inflammatory cells, up-regulation of inflammatory cytokines, intraglomerular thrombosis, induction of apoptosis, and tubular obstruction with necrotic cells and debris [42, 45, 46]. Activation of pro- and anti-inflammatory mechanisms is believed to play a key role in the induction of sepsis [47].

Activation of the innate immune response takes place after initial host-microbial encounter, which coordinates a defensive response involving both humoral and cellular components [48]. This leads to activation and secretion of various cytokines, most importantly interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and IL-6 that progress to a state of cytokine storm, hemodynamic instability, and eventually organ dysfunction and septic shock [42].

Lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, is a potent and rapid activator of a variety of cell types such as leukocytes, monocytes, and macrophages [49]. Activation of inflammatory cells by LPS constitutes the first step in a cascade of events that lead to the manifestation of Gram-negative sepsis. LPS initiates multiple intracellular signaling events, including the activation of nuclear factor-κB (NF-κB), which ultimately leads to the synthesis and release of a number of pro-inflammatory mediators, including IL-1, IL-6,IL-8, and TNF-a. The pathway that leads to activation of NF-κB has been shown to be mediated by members of the toll-like receptors (TLRs), a family of transmembrane proteins that play an important role in the defense against pathogenic microbial infection [50]. In the setting of sepsis, there is a significant up-regulation of TLRs, in particular TLR-2 and TLR-4 expression [51]. Both TLR-2 and TLR-4 are activated by LPS in a response that depends on LPS-binding protein and is enhanced by CD14 [49, 52]. An overview of the TLR signaling pathway is depicted in **Figure 1** [53]. **Figure 2** depicts the key pathways involved in the clinical course of sepsis that also have implications in the pathophysiology of sepsis-induced AKI [42].

Modulation of TLRs may become a novel therapeutic target in the treatment of organ dysfunction associated with sepsis including AKI. Similarly, cytokine adsorption to the membrane during continuous renal replacement therapy may emerge as a treatment modality in patients with sepsis and AKI [54].

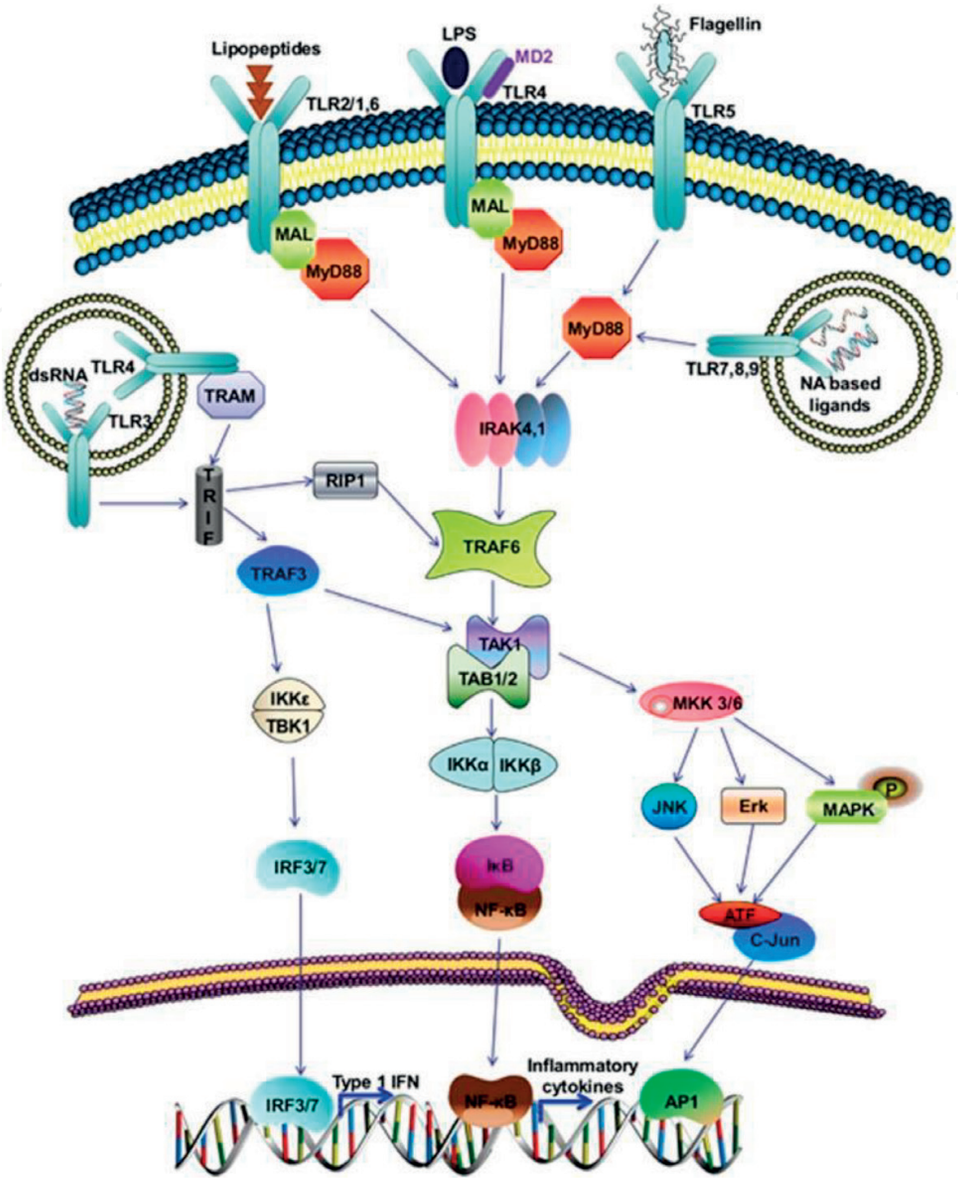

Figure 1. Toll-like receptor (TLR) signaling pathway. When TLRs are stimulated by their respective ligands, they dimerize and recruit downstream adaptor molecules, such as myeloid differentiation primary-response protein 88 (MyD88), MyD88-adaptor-like (MAL), toll/interleukin (IL)-1 receptor (TIR)-domain-containing adaptor-inducing interferon-β (TRIF), TRIF-related adaptor molecule (TRAM), which activate other downstream molecules leading to the activation of signaling cascades that converge at the nuclear factor-κB (NF-κB), interferon (IFN) response factors (IRFs), and mitogen-activated protein (MAP) kinases. These molecules induce the transcription of several pro-inflammatory molecules, such as interleukin (IL)-6, IL-8, IL-12, and tumor necrosis factor-α (TNF-α). AP1, activator protein 1; ATF, activating transcription factor; dsRNA, double-stranded RNA; ERK, extracellular signal-regulated kinase; IKK, inhibitor of kappa light polypeptide gene enhancer in B-cell kinase; IRAK, IL-1 receptor-associated kinase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MD, myeloid differentiation factor; MKK, MAPK kinase; NA, nucleic acid; TAB, transforming growth factor-β-activated kinase 1/MAP3K7-binding protein; TAK, transforming growth factor-activated kinase; TRAF, tumor necrosis factor receptor-associated factor; RIP1, receptor-interacting protein 1. Adapted from Anwar et al. [53].

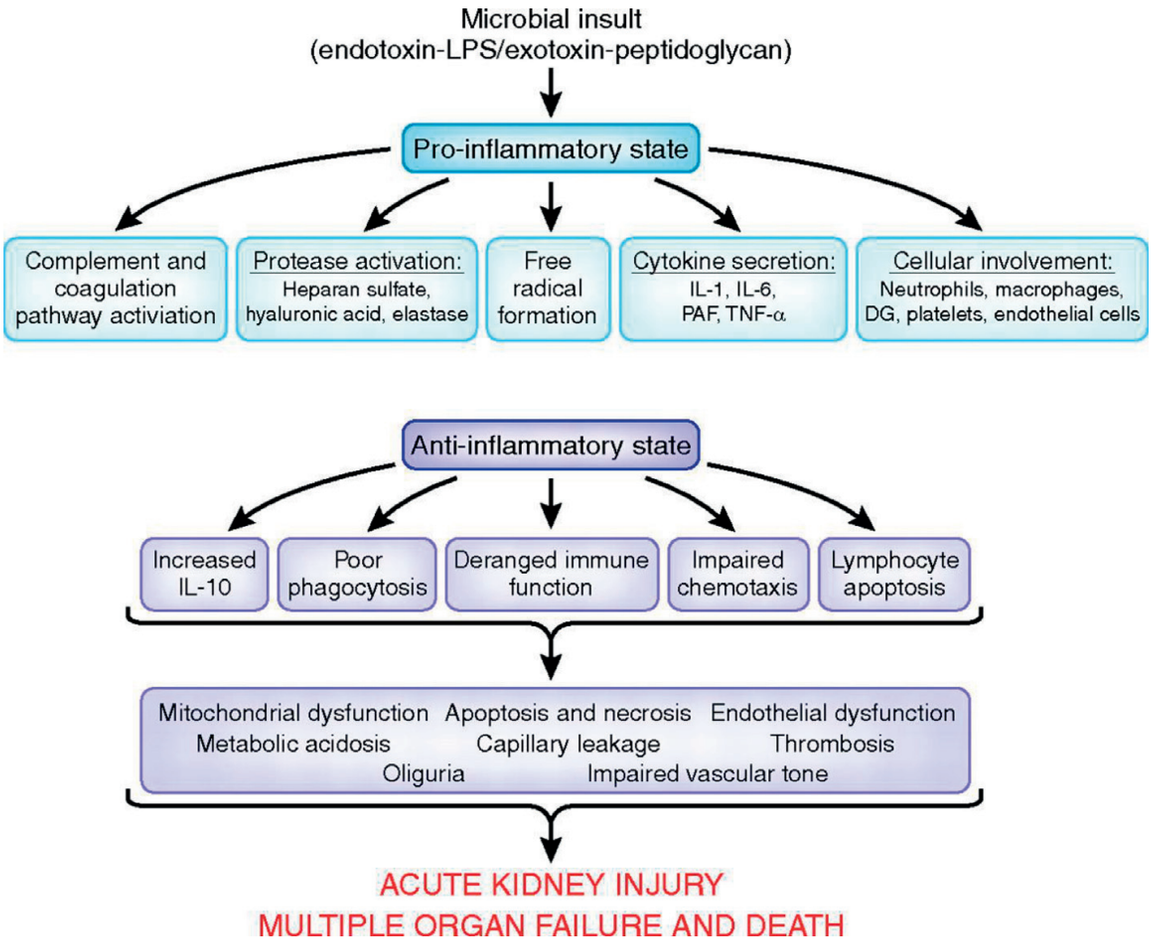

Figure 2. Key pathogenic pathways involved in sepsis that also have implications in the pathophysiology of sepsis-induced acute kidney injury. Adapted from Zarjou and Agarwal [42].

5. Clinical presentation of acute kidney injury

The clinical presentation of AKI depends on the cause and severity of renal insult. Mild to moderate AKI is asymptomatic and patients are identified based on laboratory testing. However, patients with severe AKI often present with a variety of symptoms including fatigue, anorexia, nausea, vomiting, restlessness, confusion, fluid retention, and weight gain. Severe and prolonged AKI may cause central nervous system manifestations such as uremic encephalopathy with asterixis, confusion, and seizure; bleeding tendency due to platelet dysfunction and severe anemia. Patients with AKI may have normal urine output, oliguria (urine output less than 400 mL/24 h) or anuria (urine output less than 100 mL/24 h).

6. Diagnosis of acute kidney injury

History and physical examination, with an emphasis on assessing the patient's volume status, are crucial for determining the cause of AKI. The history should inquire about the use of nephrotoxic medications or presence of systemic illnesses that might impair renal perfusion or directly impair renal function. Physical examination should assess the intravascular volume status and any skin rashes that indicate systemic diseases. The initial laboratory evaluation should include urinalysis, urine microscopy, complete blood count, electrolytes, serum creatinine or cystatin C level, and fractional excretion of sodium (FENa). Urinalysis and urine microscopy are essential in the initial work up of AKI. Findings on urinalysis and urine microscopy guide the differential diagnosis and direct further investigation. Imaging studies in particular ultrasonography can help in the initial work up of AKI. Ultrasonography is particularly important in older men with AKI who may have bladder outlet obstruction as a result of prostate hypertrophy [55, 56]. Renal biopsy is reserved for patients with AKI where the cause is not clear. Renal biopsy is particularly important when there is suspicion of an underlying disease that requires specific therapy such as glomerulonephritis or interstitial nephritis. Renal biopsy should be performed urgently in cases of rapidly progressive glomerulonephritis as indicated by rising serum creatinine or cystatin C and presence of red blood cell casts or dysmorphic red blood cells on urine microscopy.

7. New biomarkers for the quick detection of acute kidney injury

Although the RIFLE and AKIN criteria, based on serum creatinine and urine output, were a step forward in diagnosing AKI, a reliable tool to differentiate between true parenchymal and prerenal azotemia in clinical practice is still lacking [57]. Lately, several papers on the use of new urinary and serum biomarkers for the diagnosis and prognostication of AKI have been published with the hope that these biomarkers will lead to a new era of earlier diagnosis, better prognostication and treatment. Some of the studied biomarkers are listed in **Table 4**. Although these biomarkers may help to understand some of the biochemical and biological processes during AKI, their utility in preventing and treating AKI at present is at most very limited [58].

Acronym	Legend	Main source
AP	Alkaline phosphatase	Liver, bone, intestine, placenta, brush border proximal convoluted tubules
α_1MG	Alpha 1 microglobulin	Liver. Reabsorption by renal proximal tubular cells
$\alpha_1$acidGP	Alpha 1 acid glycoprotein	Liver. Reabsorption by renal proximal tubular cells
B_2MG	Beta 2 microglobulin	All nucleated cells. Reabsorption by renal proximal tubular cells
Cystatin C	Cystatin C	All nucleated cells. Reabsorption by renal proximal tubular cells
FENA	Fractional excretion of sodium	
GGTP	Gamma glutamyl transpeptidase	All cells except myocytes. Mainly liver and kidney (brush border proximal convoluted tubules and loop of Henle)

Acronym	Legend	Main source
αGST	Alpha-glutathione S-transferase	Expressed in almost all tissues. Kidney: proximal tubular cells (cytoplasmatic)
πGST	Pi glutathione S-transferase	Expressed in almost all tissues. Kidney: distal tubular cells (cytoplasmatic)
HGF	Hepatocyte growth factor	Mesenchymal cells
IL-6	Interleukin 6	T lymphocytes, macrophages, endothelial cells, monocytes
IL-8	Interleukin 8	Monocytes, macrophages, epithelial cells, endothelial cells
IL-10	Interleukin 10	Monocytes, lymphocytes, macrophages
IL-18	Interleukin 18	Monocytes, dendritic cells, macrophages and epithelial cells
KIM-1	Kidney injury molecule 1	Kidney: proximal tubular cells
LFABP	Liver-type fatty acid-binding protein	Hepatocytes, kidney: proximal tubular cells
NGAL	Neutrophil gelatinase-associated lipocalin	Leucocytes, loop of Henle and collecting ducts
NAG	*N*-Acetyl beta glucosaminidase	Several tissues (liver, brain, spleen, etc.). Kidney: proximal tubular cells (lysosomal)
PAI-1	Plasminogen activator inhibitor 1	Endothelium
PCX	Podocalyxin	Podocytes
RBP	Retinol-binding protein	Liver. Reabsorption by renal proximal tubular cells
sTNFR-I	Soluble tumor necrosis factor receptor I	Most cells and tissues (cytotoxic, apoptotic, and pro-inflammatory effects)
sTNFR-II	Soluble tumor necrosis factor receptor II	Most cells and tissues (proliferative and anti-apoptotic effects)
TNF-α	Tumor necrosis factor alpha	Macrophages, lymphoid cells, renal parenchymal cells
11 k-TXB_2	11-keto-Thromboxane B_2	Platelets
vWF	Von Willebrand factor	Endothelium, megakaryocytes, subendothelial connective tissue
TIMP-2	Tissue inhibitor of metalloproteinase-2	Ubiquitous expression. Renal tubular cells
IGFBP7	Insulin-like growth factor-binding protein 7	Ubiquitous expression. Renal tubular cells

Adapted and modified from Vanmassenhove [57].

Table 4. Urinary and serum biomarkers for the diagnosis of acute kidney injury.

8. Management of acute kidney injury

Management of AKI mandates close collaboration among nephrologists and other physicians involved in the care of the patient. The clinical evaluation of AKI includes a careful history and thorough physical examination. Drug history should include over-the-counter medications, herbal remedies, and recreational drugs [59]. Once established, management of AKI is mainly

supportive. Most patients with AKI should be hospitalized unless the condition is mild and attributed to an easily reversible cause. The evaluation and initial management of patients with AKI should include: (1) an assessment of the contributing causes of the kidney injury, (2) an assessment of the clinical course including comorbidities, (3) a careful assessment of volume status, and (4) the institution of appropriate therapeutic measures designed to reverse or prevent worsening of functional or structural kidney abnormalities [60]. The initial assessment of patients with AKI should include the differentiation between prerenal, renal, and postrenal causes [34, 61–63]. In the majority of cases, the exclusion of postrenal causes using ultrasonography is an established approach and sufficient for the initial assessment. Differentiation between prerenal and renal causes is more challenging as renal hypoperfusion may coexist with any stage of AKI.

Assuring adequate renal perfusion by achieving and maintaining hemodynamic stability and avoiding hypovolemia is crucial in the initial management of AKI. Measurement of central venous pressures may be helpful in case of difficulty in assessing intravascular volume. Prerenal azotemia is rapidly reversible when the underlying cause is corrected [34, 60–63]. It is important to point out that certain elements of the definition of prerenal azotemia have diagnostic limitations. In the setting of renal hypoperfusion, compensatory mechanisms aimed at maintaining GFR may become operative. These compensatory mechanisms include efferent arteriolar vasoconstriction, afferent arteriolar dilation, and neuro/hormonal changes that lead to increased tubular reabsorption of solutes and water [64]. This implies that patients with renal hypoperfusion may be classified as having AKI by urine output criteria without having a significant change in serum creatinine concentration.

Volume resuscitation can correct prerenal conditions resulting from absolute or relative hypovolemia. However, renal hypoperfusion resulting from low cardiac output (severe cardiomyopathy) and reduced renal perfusion pressure (sepsis, or end-stage liver disease) cannot always be corrected by fluid administration [60]. Isotonic solutions (e.g., 0.9 sodium chloride) are preferred over hyperoncotic solutions due to the detrimental effect of these solutions (e.g., dextrans, hydroxyethyl starch, and albumin) [65, 66]. The use of hydroxyethyl starch as a plasma-volume expander has been shown to be an independent risk factor for AKI in patients with severe sepsis or septic shock [65]. In patients with persistent hypotension, vasopressors may be needed to maintain a mean blood pressure of 65 mmHg [66].

9. Pharmacologic interventions for management of acute kidney injury

A number of pharmacologic interventions have been evaluated in the early management of AKI. Some have been designed to improve renal perfusion and others to modulate intrarenal pathophysiology. In patients with hyperdynamic septic shock, both norepinephrine and terlipressin were effective in raising mean arterial blood pressure (MAP) leading to an improvement in renal function [67].

Low-dose (renal-dose) dopamine was frequently used in the ICU setting for its presumed renoprotective effects. Low-dose dopamine may increase the urine output on the first day of

use, but prospective and retrospective studies as well as several meta-analyses have not shown positive effect in prevention of AKI or improvement in renal function in patients with AKI [68–71]. To the contrary, low-dose dopamine has been shown to worsen renal perfusion in patients with established AKI [72]. Therefore, the routine use of low-dose dopamine in critically ill patients should be abandoned.

Randomized controlled trials of early AKI and contrast nephropathy studying fenoldopam, a selective dopamine A1 agonist, proved this agent is ineffective at protecting renal function or reducing the need for renal replacement [73, 74]. Fenoldopam has been shown, however, to lower the risk of AKI in cardiac and major surgery patients according to some meta-analyses, without an effect on renal replacement or hospital mortality [75, 76]. In most of these studies, fenoldopam was associated with hypotension.

High-chloride fluids may be associated with increased risk of AKI and mortality in patients with sepsis [77]. Early goal-directed therapy with close monitoring of central venous pressure, mean arterial pressure, and oxygen saturation has been shown to be protective against AKI in patients admitted to the intensive care unit with sepsis [78, 79].

Atrial natriuretic peptide (ANP) is produced by cardiac atrial myocytes in response to atrial distension or increased atrial pressure. It induces afferent dilatation and efferent vasoconstriction, thereby increasing glomerular filtration and urinary sodium excretion [80]. B-type (brain) natriuretic peptide (BNP) is primarily produced in the cardiac ventricles and has similar effects [81, 82]. Low doses of recombinant human ANP-enhanced renal excretory function, decreased the probability of dialysis, and improved dialysis-free survival in early, ischemic acute renal dysfunction after complicated cardiac surgery [83]. Similar effects were observed in patients undergoing liver transplantation [84, 85]. However, larger doses of ANP were not effective in improving dialysis-free survival or reduction in dialysis in large randomized clinical trials [86, 87].

Theophylline, an adenosine antagonist has been shown in several preliminary reports to be beneficial in the prevention of contrast nephropathy and cisplatin nephrotoxicity [88–90]. A few adjunctive agents such as flavonoids (silymarin) and carotenoids (lycopene), have been tried in pilot studies in cancer patients receiving cisplatin with limited success in some but not all studies [91–93]. Adequately powered, controlled studies to support the efficacy of these agents are lacking.

Levosimendan, a calcium sensitizer, has inodilator, cardioprotective, and anti-inflammatory effects [94]. Two meta-analyses suggested that the use of levosimendan was associated with a reduction of renal replacement therapy in critically ill patients and patients undergoing cardiac surgery [95, 96]. The studies in both meta-analyses were small, heterogeneous, and AKI was not always a predefined endpoint.

The role of loop diuretics and osmotic agents in the prevention and treatment of AKI in humans has been disappointing despite their ability to decrease the tubular oxygen consumption and relieve intratubular obstruction in animal models [97–99]. A metanalysis has shown that frusemide was not associated with any significant clinical benefits in the prevention and treatment of AKI in adults, in addition to the concern of increased risk of ototoxicity associated with high doses [100].

N-acetyl-cysteine, a thiol-containing antioxidant has been investigated in several trials, mainly in the prevention of contrast-induced nephropathy. Despite some positive reports [101, 102], the protective effect of N-acetyl-cysteine is still controversial [103–106]. Similarly, N-acetyl-cysteine was not found to be protective against other causes of AKI particularly in hypotensive patients in the ICU or patients undergoing cardiac surgery [107, 108]. Hydration with sodium bicarbonate, as compared to normal saline, has been shown in some studies to be superior to normal saline in the prevention of contrast-induced nephropathy [109–111]. Other studies have shown no superiority of sodium bicarbonate over saline in the prevention of contrast nephropathy [112, 113]. Hydration with isotonic solutions either normal saline or sodium bicarbonate in addition to the use of low osmolar contrast agents is the most effective strategy to prevent contrast-induced nephropathy.

Statins may have a beneficial effect in high-risk patients exposed to contrast administration for angiography. In a randomized multicenter clinical trial, the short-term use of rosuvastatin was found to be protective against contrast nephropathy in diabetic patients with concomitant CKD who underwent coronary/peripheral arterial angiography [114]. In another single center trial high-dose rosuvastatin (40 mg on admission followed by 20 mg daily) given to statin-naïve patients with acute coronary syndrome who were scheduled for an early invasive procedure was protective against contrast-induced AKI and improved the short-term clinical outcome [115]. 6.7% of patients in the early high-dose rosuvastatin group developed AKI compared to 15.1% in the control group. The 30-day rate of adverse cardiovascular and renal events was also reduced in the rosuvastatin group (3.6 versus 7.9%). In a subgroup analysis of this study, rosuvastatin had a protective effect among female diabetic patients with CKD [116]. Similarly, a single high dose of atorvastatin (80 mg) administered within 24 h before exposure to intravenous contrast was effective in reducing the rate of AKI in diabetic patients with renal dysfunction [117, 118]. The protective effect of statins has been confirmed in multiple meta-analyses [119–121]. However, the beneficial effect of statins in patients undergoing coronary interventions was not observed in patients undergoing cardiac surgery. In this group of patients, the use of statin either showed no benefit or was detrimental [122–124].

10. Renal replacement therapy for acute kidney injury

There is a wide variation in clinical practice relating to the indication for and timing of RRT for patients with AKI. There is also no agreement on the selection of the specific modality of RRT and prescription of intensity of therapy. Among the several modalities of RRT, continuous renal replacement therapy has become very popular, especially in the ICU setting where patients may be hemodynamically unstable to tolerate intermittent hemodialysis. There does not appear to be a significant difference in either mortality or recovery of renal function associated with the various modalities of RRT. This is discussed in details in other sections of the book designated for RRT.

11. Prevention of acute kidney injury

Acute kidney injury is particularly common in ICU patients affecting more than 50% and is associated with increased mortality and morbidity [16]. The Working Group on Prevention, AKI section, European Society of Intensive Care Medicine has recently issued recommendations for the prevention of AKI, specifically addressing the role of fluids, diuretics, inotropes, vasopressors/vasodilators, hormonal and nutritional interventions, sedatives, statins, remote ischemic preconditioning, and care bundles as shown in **Table 5** [125]. The recommendations are summarized as follows: timely resuscitation with fluids, vasopressors, and inotropic agents remains the cornerstone in the prevention of AKI. Volume expansion with isotonic crystalloids is reserved for true and suspected hypovolemia. The use of starches and dextrans should be avoided. In hypotensive patients, vasoconstrictors, preferably norepinephrine, should be administered with or following volume expansion. Mean arterial pressure (MAP) of 65–70 mmHg is adequate in most patients except in cases of preexisting chronic hypertension where a higher MAP (80–85 mmHg) should be targeted. Review of all medications and cessation of nephrotoxic agents is mandatory. Diuretics should not be used for prevention of AKI but may benefit in cases of volume overload and congestion. Hyperglycemia should be avoided. The effect of statins appears to depend on the setting, with promising results in contrast administration but no effect or even harm in cardiac surgery patients [125].

Volume expansion

Controlled fluid resuscitation in volume depletion, while, however, avoiding volume overload (1 C)

Avoidance of starches, gelatine, and dextrans (2C)

Correction of hypovolemia/dehydration using isotonic crystalloids in patients receiving intravascular contrast media (1 B)

Regular monitoring of chloride levels and acid–base status in situations where chloride-rich solutions are used (BPS)

Use of balanced crystalloids for large volume resuscitation (2C)

Use of human albumin if necessary for the treatment of patients with septic shock (2C).

Use of diuretics

No loop diuretics for the prevention of AKI (Grade 1B)

Diuretics to control or avoid fluid overload in patients that are diuretic-responsive (Grade 2D)

Use of vasopressors

Titrating vasopressors to a MAP of 65–70 mmHg (Grade 1B) in patients with septic shock and to (80–85 mmHg) for patients with chronic HTN (Grade 1C).

lowering SBP to 140–190 mmHg in patients with acute cerebral hemorrhage with severe admission hypertension (Grade 1C)

Norepinephrine as the first-choice vasopressor to protect kidney function (Grade 1B) and vasopressin in patients with vasoplegic shock after cardiac surgery (Grade 2C).

Individualizing target pressure when premorbid blood pressure is available (BPS)

Use of vasodilators
No low-dose dopamine for protection against AKI (Grade 1A)
No levosimendan for renal protection in patients with sepsis and in cardiac surgery patients with poor preoperative left ventricular function (Grade 1B).
No fenoldopam or natriuretic peptides for renal protection in critically ill or cardiovascular surgery patients at risk of AKI (Grade 2B).
Sedatives
Shorter sedation using propofol or dexmedetomidine (BPS)
Hormonal manipulation
Target a blood glucose level of at least below 180 mg/dL (10 mmol/l) (Grade 2B).
Use of erythropoietin or steroids (Grade 2 B)
Metabolic interventions
Avoid using high-dose IV selenium for renal protection in critically ill patients (1B)
Avoid using N-acetylcysteine to prevent contrast-associated AKI in critically ill patients (Grade 2B)
Provide adequate nutritional support preferably through the enteral route (BPS)
Statins
Avoid the use of high-dose statins to prevent postoperative AKI in cardiac surgery (Grade 1A)
Use atorvastatin or rosuvastatin to prevent contrast-associated AKI in high-risk patients undergoing coronary contrast angiography (Grade 2B)
Remote ischemic preconditioning
Do not use remote ischemic preconditioning for prevention of AKI in critically ill patients
AKI care bundles
Use of the KDIGO recommendations to reduce the incidence of AKI after cardiac surgery (Grade 2C).
Use of AKI care bundles outside the intensive care unit has some benefits, including the potential to improve the outcome of AKI (BPS).

AKI, acute kidney injury; HTN, hypertension; MAP, mean arterial pressure; BPS, best practice statement.

Table 5. Expert opinion of the Working Group on Prevention, AKI section, European Society of Intensive Care Medicine [125].

12. Prognosis of acute kidney injury

With the advent of agreed definition and classification of AKI based on changes in serum creatinine and urine output, there is now increasing awareness of the poor prognosis following AKI. Multiple studies have shown that patients with AKI are at high risk for progression to advanced stage CKD and death following hospital discharge. In a meta-analysis of 13 cohort studies comparing the risk of CKD, ESRD, and death in patients with and without AKI, the pooled incidence of CKD and ESRD were 25.8/100 person-years and 8.6/100 person-years, respectively [8]. Patients with AKI had higher risks of developing CKD (pooled adjusted hazard ratio 8.8), ESRD (pooled adjusted HR 3.1), and mortality (pooled adjusted HR 2.0) than patients without AKI [8]. In another meta-analysis of 48 studies containing 47,107 patients

between 1985 and 2007 the incidence rate of mortality was 8.9 deaths/100 person-years in survivors of AKI compared to 4.3 deaths/100 patient-years in survivors without AKI (rate ratio 2.59) [126]. The incidence rate of CKD after an episode of AKI was 7.8 events/100 patient-years, and the rate of ESRD was 4.9 events/100 patient-years [126]. In an observational cohort study with a median follow-up of 9 years the intermediate-term (30–364 days) adjusted mortality HRs for AKI versus no AKI were 2.48, 2.50, 1.90, and 1.63 for baseline eGFRs ≥60, 45–59, 30–44, and <30 mL/min/1.73 m^2, respectively [127]. This indicates that baseline renal function is an important determinant factor for outcome following an episode of AKI. A retrospective cohort study showed that patients who developed AKI during a hospitalization were at substantial risk for the development of CKD in the following year, and the timing of recovery was a strong predictor, even for the mildest forms of AKI [128].

The multinational AKI-EPI study on ICU patients in 97 centers showed that increasing AKI severity was associated with increased mortality, and AKI patients had worse renal function at the time of hospital discharge [16].

According to the United States Renal Data System, acute tubular necrosis (ATN) without recovery as a cause of ESRD increased from 1.2% in 1994 to 1998 to 1.7% in 1999 to 2003 [129]. The incidence will likely continue to rise with the aging population and increase in comorbidities in patients admitted to the ICU.

Risk factors associated with progressing to CKD among AKI survivors have been identified and include advanced age, diabetes mellitus, decreased baseline glomerular filtration rate, severity of AKI, and a low concentration of serum albumin [6, 130].

13. Conclusion

Acute kidney injury, previously named acute renal failure, is characterized by abrupt deterioration in renal function. The incidence of AKI has lately increased, both in the hospital and community setting. Management of AKI involves fluid resuscitation, avoidance of nephrotoxic agents, adjustment of medications, and correction of fluid, acid-base and electrolyte imbalance. Depending on the severity of renal insult, AKI may require renal replacement therapy in the form of dialysis or continuous renal replacement. Despite all the advances in the field, AKI still carries a high mortality and long term consequences. Recognition of risk factors, early diagnosis, and management of AKI are crucial to improve the long-term patient's outcome.

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