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Perioperative Acute Kidney Injury and Anesthesia: A Narrative Review

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ABSTRACT

Perioperative acute kidney injury (AKI) remains challenging for the anesthesiologist and surgeon. It is one of the most common, heterogeneous, and severe complications. Perioperative AKI is associated with increased morbidity, mortality, the need for renal replacement therapy (RRT), prolonged hospital stays, and escalating costs and healthcare resource utilization. Concomitant comorbidities, age, size, type, timing, the urgency of surgery, improper fluid management, anemia, hyperglycemia, malnutrition, the use of blood and blood products, contrast dyes, diuretics, and exposure to nephrotoxins are the main factors in the development of AKI. The main factors involved in the pathogenesis of perioperative AKI are highly complex and include a combination of hypoperfusion, microcirculatory and endothelial dysfunction, inflammation, and tubular cell damage. The main aim of anesthesiologists should be to identify risk factors in the perioperative period and minimize the incidence of perioperative AKI through appropriate anesthesia management and the necessary protective and preventive strategies. The anesthesia management should include optimization of hemodynamics, adequate organ perfusion and oxygenation, suitable monitoring, correct fluid management, anesthesia, pain control, mechanical ventilation methods, glycemic control, avoiding nephrotoxic drugs, contrast dyes, and blood transfusions, and early RRT and nutritional support. New biomarkers should be used to detect, intervene, and treat AKI promptly. We review the recent literature on the value and importance of comprehensive preoperative evaluation, optimization of risk factors, perioperative monitoring, anesthesia and pain management, preventive methods, and treatment in patients with AKI.

Keywords: Perioperative period, acute kidney injury, preoperative evaluation, optimization, anesthesia management, multidisciplinary approach.

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INTRODUCTION

Perioperative AKI is one of the most common, heterogeneous, and severe complications. Despite significant advances in anesthesia and surgery in recent years, perioperative AKI remains a significant risk factor for increased mortality, morbidity, need for RRT costs, and prolonged hospital stay. Therefore, it is crucial to quickly recognize, prevent, diagnose, and treat perioperative AKI.[1–3] The overall incidence of AKI among all hospital admissions is known to affect 15% of hospital admissions; the incidence of perioperative AKI varies between 18% and 47%, the incidence in intensive care unit (ICU) patients reaches 50%, and AKI-related mortality is 23%.[2–4]

Perioperative AKI is a common complication after major surgery, with the highest risk primarily in cardiac and transplantation surgeries, especially liver, followed by general, thoracic, orthopedic, vascular, and urological surgeries.[1,2–4]

In 2012, the KDIGO (Kidney Disease: Improving Global Outcomes) guideline was created by combining the RIFLE criteria (Risk, Injury, Failure, Loss of Renal Function, and End-Stage Renal Failure=ESRF) and the AKIN criteria (Acute Kidney Injury Network), revising the diagnostic criteria for AKI.[5] KDIGO guidelines define AKI as ≥0.3 mg/dL rise in serum creatinine (sCr) over 48 hours, a ≥50% rise in sCr over 7 days, or decreased urine output (UO) of less than 0.5 mL/kg/hour over 6 hours.[6]

AKI was classified according to staging based on sCr value and UO per hour. The damaged kidney was determined as AKI, chronic kidney disease (CKD), and end-stage kidney disease (ESKD). AKI is divided into stages 1, 2, and 3 based on individualized risk factors.[7] Depending on time, the first 7 days are defined as AKI, between 7 days and 3 months as acute kidney disease (AKD), and after 3 months as chronic kidney damage.[7–10]

Our review focuses on comprehensive preoperative preparation, optimization of risk factors, perioperative monitoring, anesthesia and pain management, preventive methods, and treatment in patients with AKI in light of the literature.

Etiology of Acute Kidney Injury

The etiology of AKI depends on prerenal (21%), intrinsic (62%), and postrenal (10%) causes. The causes of AKI are a decrease in cardiac output (CO) and mean arterial pressure (MAP) in the prerenal category, intrinsic (glomerular, tubular-interstitium, vascular causes), and postrenal causes due to obstruction. The etiological causes of perioperative AKI are summarized in Table 1.[1,4,9,10]

Pathogenesis in Acute Kidney Injury

The pathophysiology of perioperative AKI is a highly complex and dynamic process that depends on many factors. These significant factors include renal hypoperfusion, microcirculation and endothelial dysfunction, microvascular thrombus formation, inflammation due to cytokine release, tubular cell damage, obstruction, renal venous congestion, and intra-abdominal hypertension. The leading causes of renal hypoperfusion are decreased volume and CO, systemic vascular resistance (SVR), MAP, and increased renal arterial resistance.[1,4,9–11] The primary causes of volume depletion may be bleeding, vomiting, diarrhea, polyuria, burns, sepsis, and capillary leak syndromes. Low CO may be due to congestive heart failure (CHF), cardiac tamponade, cardiogenic shock, pulmonary hypertension, and sepsis. Low SVR may result from sepsis, cirrhosis, and anaphylaxis. Finally, increased renal arterial resistance may occur secondary to renal hypoperfusion, medications, radiocontrast administration, and, less commonly, hepatorenal syndrome. For these reasons, while perfusion in the kidneys continues, the glomerular filtration rate (GFR) remains constant due to the stimulation of the sympathetic nervous system with the release of angiotensin-II (activation of the renin-angiotensin-aldosterone system=RAAS) and antidiuretic hormone (ADH). In the later period, vasoconstriction occurs in afferent and efferent arterioles due to extended periods of hypoperfusion, causing a gradual reduction in GFR. Patients with poor renal function because of conditions such as hypertensive and diabetic nephropathy in the preoperative period have a higher risk of a more rapid decline in GFR.[10–14] As levels of angiotensin II increase, vasoconstriction develops in both afferent and efferent arterioles in the glomerulus, leading to reduced GFR. This can cause a more rapid decline in GFR, initiating a vicious cycle.[14] Renal autoregulation mechanisms may not always maintain appropriate glomerular pressure.[15]

The second critical step in perioperative AKI is inflammation.[10,11,16] Inflammation in the renal tubules causes leukocyte migration and subsequent disruption of microcirculation with endothelial dysfunction. Renal epithelial cells are vulnerable to localized and systemic inflammation.[10,11,17] This vulnerability can be mainly attributed to the accumulation of nephrotoxins in endothelial cells and basal cellular oxygen consumption. Loss of adenosine triphosphate (ATP) causes impairment of cellular functions and subsequent apoptosis or necrosis. Injury and inflammation in endothelial cells also cause changes in cellular structure and cytoskeleton. In addition, a loss of cellular polarization develops with a deterioration in cellular transport and barrier properties. As a result of cell death, necrotic cell byproducts accumulate in the tubular lumen, resulting in lumen obstruction.[10,18–20]

As perioperative AKI develops, inflammation and damage to endothelial cells cause irreversible microvascular dysregulation in the renal tubule.[18] It also contributes to arteriolar vasoconstriction by releasing endothelin-1, angiotensin II, thromboxane A_2, prostaglandin F_2, and sympathetic activation.[18–20] Bradykinin, nitric oxide (NO), and acetylcholine (Ach) cause arteriolar vasodilation. This balance turns in favor of vasoconstriction. However, this also increases the production of intercellular adhesion molecules (ICAM-1) in compromised endothelial cells. ICAM-1 stimulates leukocytes, causing further local inflammation in the kidney tissue and blockage of smaller vessels. Many locally secreted inflammatory mediators play a role in the developmental pathogenesis of AKI, among which the most potent mediators are tumor necrosis factor-α (TNF-α), transforming growth factor beta (TGFb), interleukin-1β, interleukin-6, interleukin-8,

Table 1. Etiological causes of perioperative acute kidney injury (AKI)

Prerenal etiologies of perioperative AKI	
Preoperative	**Intraoperative**
1. Hypovolemia	1. Hypovolemia
2. Gastrointestinal losses	a. Insensible Losses
a. Hemorrhage	b. Hemorrhage
b. Third spacing	c. Overdiuresis
3. Sepsis	2. Hypotension due to low SVR (anesthesia induced)
4. Heart failure	3. Low CO (heart failure, anesthesia, and CPB induced)
5. Increased IAP	4. Increased IAP
6. Cirrhosis, HRS	5. Aortic cross-clamp time
Intrinsic etiologies of perioperative AKI	
• Inflammation	
• Patient Comorbidities: CKD, DM, obesity, atherosclerosis	
• Drug-induced: ACEinh, antibiotics, aspirin, phenytoin, furosemide, NSAIDs, clopidogrel, tacrolimus, chemotherapeutic agents	
• Radiocontrast-Dye Agents	
• Endogenous Nephrotoxins: Hemoglobin and myoglobin	
• Acidosis	
• Infection	
• CPB	
• Anemia	
• PRBCs administration	
• Fluid solutions (hydroxyethyl starch, chloride-rich solutions)	
Postrenal etiologies of perioperative AKI	
Preoperative	**Intraoperative**
Tumor	Surgical Intervention or damage
Prostatic enlargement	
Calculi	
Blood clots	
Neurogenic bladder	

IAP: Intra-abdominal pressure; HRS: Hepatorenal syndrome; SVR: Systemic vascular resistance; CO: Cardiac output; CPB: Cardiopulmonary bypass; CKD: Chronic kidney disease; DM: Diabetes mellitus; NSAIDs: Nonsteroidal anti-inflammatory drugs; ACEinh: Angiotensin-converting enzyme inhibitors; PRBCs: Packed red blood cells.

toll-like receptor 4 (TLR4), danger-associated molecular pattern molecules (DAMPs), pathogen-associated molecular patterns (PAMPs), and C-C motif chemokine 2 (Fig. 1).[10,11,18–20]

Preoperative Risk Factors and Risk Stratification

Preoperative existing comorbidities and risk factors contribute significantly to the occurrence of perioperative AKI. Identifying and addressing the critical risk factors related to the patient and the surgery is significant in preventing AKI. These include older age, black race, female gender, obesity, previous cardiovascular or thoracic surgery, CKD, CHF, coronary artery disease (CAD), hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), obesity, peripheral vascular disease, neurological/cerebrovascular disease,

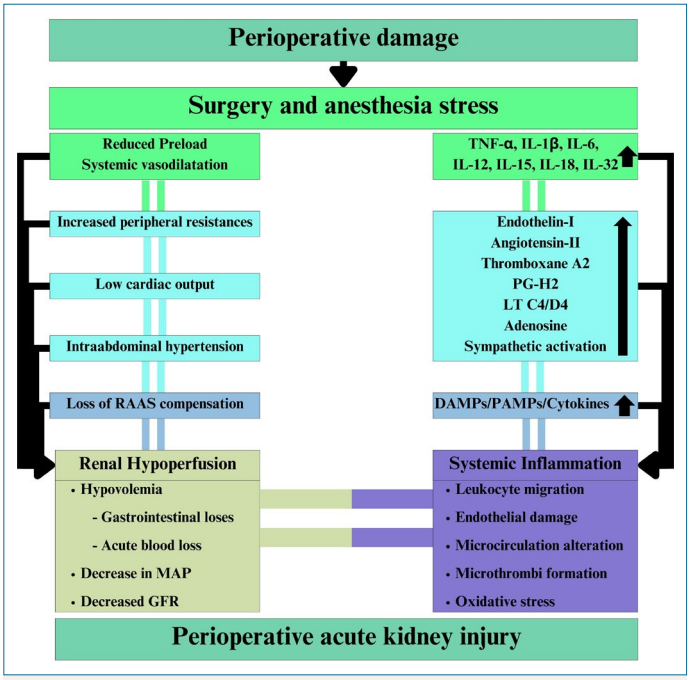

Figure 1. Pathophysiology of acute kidney injury (AKI).

RAAS: Renin-angiotensin-aldosterone system; MAP: Mean arterial pressure; GFR: Glomerular filtration rate; DAMPs: Danger-associated molecular pattern molecules; PAMPs: Pathogen-associated molecular patterns.

anemia, an ejection fraction below 30%, preoperative use of inotropes, intra-aortic balloon pump, ventilation, cardiac catheterization within 24 hours after surgery, functional dependence, ventilator dependence, smoking, bleeding, ascites, development of sepsis, and cardiogenic shock. These risk factors are summarized in Table 2.[1–4,9,10] When AKI develops, it causes many complications, especially in the heart, lungs, liver, brain, gastrointestinal system, and immune system (Fig. 2).[1–3,9,10] Preoperative evaluation is essential for optimizing essential target organ functions and ensuring ideal surgical conditions. The patient should be taken to surgery after the necessary optimization and all preparations have been made, depending on whether it is elective or emergency.[2–4,9,10]

Obesity

Obesity is a complex, chronic disease characterized by a body mass index (BMI) greater than 25 kg/m^2 and excessive adipose tissue growth. It is associated with increased morbidity and mortality due to its effects on various systems and is a significant risk factor for perioperative AKI. Obesity is closely related to metabolic syndrome and may alter renal hemodynamics, leading to conditions such as glomerulomegaly and changes in GFR termed obesity-related glomerulopathy. The incidence of AKI following gastric bypass surgery is 8.5%.[21]

Anemia and Use of Blood Products

Anemia is a significant risk factor before surgery and should be corrected as much as possible. Severe anemia reduces the oxygen-carrying capacity of the blood, thereby decreasing oxygen delivery to tissues and increasing morbidity and mortality. The risk of AKI is four times higher in patients with hemoglobin levels below 8 g/dL in the preoperative period.[22,23] Effective treatment of anemia includes iron supplementation, erythropoiesis-stimulating agents, and packed red blood cell (PRBC) transfusions. However, perioperative PRBC transfusions are also associated with increased risk of AKI. Medically correcting anemia in the preoperative period and reducing unnecessary PRBC transfusions can decrease morbidity and mortality.[24] Low hemoglobin levels may impair tissue oxygenation by reducing the blood's oxygen-carrying capacity. When medullary hypoxia develops, it plays a vital role in the development of AKI. PRBCs can lead to reduced oxygen-carrying capacity, resulting in organ damage. Therefore, patients with anemia should be advised to reduce blood loss during surgery in accordance with the current 'patient blood management' protocols and optimize their condition during the preoperative period to prevent unnecessary PRBC transfusion.[22–24]

Drugs

Management of medications used in the preoperative period is critical. The use of nephrotoxic drugs is a well-known and significant cause of prerenal, intrinsic, and postrenal AKI. Many nephrotoxic drugs and drug combinations increase the risk of perioperative AKI: These include agents such as angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin-II receptor blockers (ARBs), diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), dextrans, contrast dyes, inotropes, beta-lactam antibiotics such as piperacillin-tazobactam (especially with concomitant administration of vancomycin), polymyxins/colistin, cephalosporin-aminoglycoside combinations, rifampin, amphotericin B, proton pump inhibitors, anabolic androgenic steroids, bisphosphonates, lithium, various chemotherapeutic agents, cisplatin, cyclosporine A, methotrexate, interferon, and TNF-α inhibitors.[9,10,25] To prevent AKI, in the presence of existing risk factors and comorbidities, the anesthesiologist, nephrologist, and surgical team should evaluate comprehensively with a multidisciplinary approach and apply the necessary protective and preventive strategies as much as possible.[25]

Radiocontrast-Induced Acute Kidney Injury

Contrast dye-induced AKI is a well-defined subtype of drug-induced AKI. The main events in the pathophysiology of AKI due to contrast agents are inflammation, renal vasoconstriction, endothelial dysfunction, oxidative stress, tubular cell damage,

Table 2. Important risk factors in perioperative AKI

Patient factors	
Non-cardiac surgery	**Cardiac surgery**
• Age >59	• Age >59
• BMI >32 kg/m^2	• BMI >32 kg/m^2
• CKD, DM, CHF, COPD, HT, liver disease	• DM, CHF, CKD, COPD, HT, liver disease
• Anemia	• Anemia
• EF <40%	• LV dysfunction
• Peripheral vascular disease	• Previous MI
• NSAIDs, ACEi, ARBs, diuretics, inotropes	• ACEi, ARBs, NSAIDs, diuretics, inotropes
• Smoking	• Smoking
• Previous surgery	• Previous surgery
Surgery factors	
• Emergency surgery	• Emergency surgery
• Major surgery	• Cross-clamp time
- Thorax	• Duration surgery
- Intra-abdominal	• Use of inotropes
- Peripheral vascular disease	• Hemodilution
- Transplantation	• Anemia
• Significant blood loss and fluid shift	• Hemodilution and anemia
• NSAIDs, ACEi, ARBs, diuretics, inotropes	• Off-pump CABG
	• Blood transfusion
	• IAB and LVAD use

AKI: Acute kidney injury; BMI: Body mass index; CKD: Chronic kidney disease; DM: Diabetes mellitus; CHF: Congestion heart failure; COPD: Chronic obstructive pulmonary disease; HT: Hypertension; EF: Ejection fraction; LV: Left ventricular; MI: Myocardial infarction; NSAIDs: Nonsteroidal anti-inflammatory drugs; ACEinh: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin-II receptor blockers; CABG: Coronary artery bypass grafting; LVAD: Left ventricular assist device.

and hypoxic and toxic damage.[26] Patients' risk factors should be minimized, and protective measures should be implemented to prevent the development of AKI during radiological examinations involving radiocontrast dye. Contrast dye-induced AKI is associated with increased mortality and morbidity. The main preventive strategies for contrast dye-induced AKI include maintaining normovolemia, increasing UO, administering sodium bicarbonate and N-acetyl cysteine, and discontinuing nephrotoxic agents. The risk of contrast dye-induced AKI is relatively high in patients with CKD, CHF, DM, hypertension, old age, and those who are hypovolemic. It is essential to ensure adequate blood volume before exposing these patients to drugs and contrast dye risks.[9,10,25,26]

Intraoperative Risk Factors

In most major surgeries, there is a risk of a significant reduction in adequate blood volume, mechanical obstruction, or many possible complications. Hypovolemia after anesthesia induction from the beginning of the surgery, or vasodilatation due to cava compression, low SVR, hypotension, hypoperfusion, hemodynamic instability, hypothermia, drug, toxin, contrast, tissue edema, fluid overload, abdominal hypertension, microvascular dysfunction, trauma, burn, and sepsis may contribute to the development of AKI in the perioperative period.[1–4,9,10,25,26]

Perioperative hypotension is highly common and is strongly associated with AKI. The kidneys receive 20–25% of CO.[1,14,15] Renal perfusion depends on systemic blood pressure, which is determined by CO and SVR (mean arterial pressure (MAP)=CO x SVR). Oxygen delivery, which provides oxygenation and perfusion of tissue and organs, has two components: hemoglobin, which carries the majority of oxygen, and CO.[1,15,27–29] Macrocirculation, microcirculation,

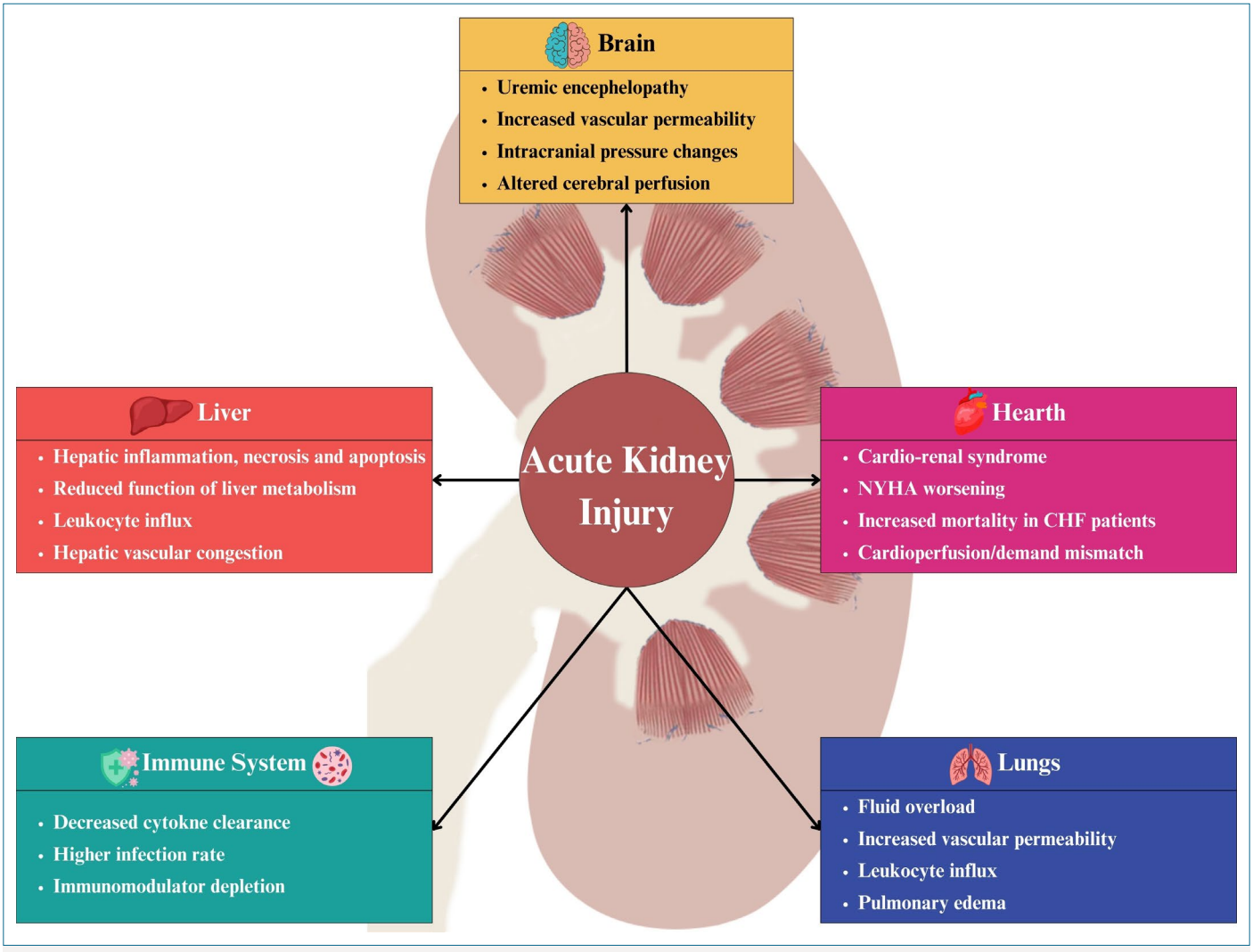

Figure 2. When AKI develops, organs and systems are primarily affected.

CHF: Congestive heart failure.

and glomerular perfusion provide renal blood flow. The determinant of macrocirculation is renal perfusion pressure (RPP), which is determined by MAP minus central venous pressure (CVP) or intra-abdominal pressure (IAP). The determinant of glomerular perfusion is glomerular perfusion pressure, which is the difference between efferent and afferent arteriolar pressures. However, autoregulation is highly important in maintaining renal flow, and MAP must be between 50–150 mmHg to prevent end-organ damage. The GFR generally does not change until MAP falls below 50 mmHg. However, when MAP falls below this level, autoregulation is disrupted, renal hypoperfusion-hypoxia develops, and oxygenation deteriorates. When GFR drops below 80 mL/min/1.73 m^2, renal blood flow decreases, UO decreases, and AKI develops.[1,15,25,27–30]

One of the critical factors that trigger AKI is hypertension. AKI may develop following inflammation, endothelial damage, and renal hypoperfusion due to excessive vasoconstriction following RAAS activation in the presence of hypertension. For this reason, it is essential to detect hypertension early, treat it, and ensure optimization during the perioperative period.[25,31]

Intra-Abdominal Pressure

Increased IAP is common after abdominal surgery. Abdominal compartment syndrome occurs when IAP increases for a long time due to fluid overload and widespread edema in the intestinal wall. As a result, there is compression on the renal vascular structure, causing renal ischemia and the development of AKI.[32] Increasing IAP can compress the renal

veins due to mechanical pressure and the renal arteries by activating the sympathetic system. As IAP increases, renal perfusion may decrease, ultimately leading to the development of AKI. Post-pneumoperitoneum (PP) during laparoscopic surgery also causes a temporary increase in IAP, resulting in a significant decrease in UO, and patients may become oliguric despite being normovolemic and normotensive. In critically ill patients with multiple comorbidities and those with CKD, PP time should be minimized as much as possible.[32,33]

Anesthesia Management

Many risk factors cause AKI in the perioperative period, among which hypotension is the most critical. The incidence of intraoperative hypotension is 41–93%.[28,29] The main factors that cause hypotension include vasodilation after induction of general or regional anesthesia, hypovolemia, mechanical ventilation, pregnancy, trauma, stress, dehydration, burns, and sepsis. Perioperative hypotension is highly common and is strongly associated with organ damage, particularly AKI. Perioperative hypotension contributes to the development of AKI, partly due to the sensitivity of the kidney, especially the renal medulla, to ischemia and hypoxia.[1,15,27–29] Prolonged episodes of hypotension during the intraoperative period may cause AKI by reducing RPP in patients with impaired autoregulation. The anesthesiologist must take all necessary protective and preventive measures to reduce the risk of AKI. The main goal in hemodynamic management should be to maintain a MAP above 65 mmHg, and maintaining normovolemia is highly important in preventing perioperative AKI. The severity and duration of hypotension are especially highly decisive; MAP below 60–70 mmHg and durations of hypotensive episodes exceeding 10 minutes are strongly associated with postoperative AKI. To maintain MAP during surgery, the use of norepinephrine as a vasopressor is recommended to increase vascular tone response, in addition to volume replacement. Therefore, it must be detected early and treated promptly according to the underlying cause.[25–30]

One of the critical factors that trigger AKI is hypoxemia. After the administration of anesthetic drugs, inflammation is triggered through hypoxia-inducible factors (HIFs) 1 and 2 in the presence of hypoxemia, along with the activation of surgical and anesthesia stress. This may contribute to the development of AKI by causing endothelial damage, oxidative stress, lipid peroxidation, apoptosis, and necrosis.[12–18] For this reason, it is essential to prevent hypoxemia in the perioperative period, improve the patient's oxygenation, and provide adequate preoxygenation during anesthesia induction.[11,25,34]

Patients with DM have a much higher risk of developing AKI due to hyperglycemia, insulin resistance, increased free fatty acids, and inflammation. Therefore, blood glucose regulation in the preoperative period is critical to prevent the development of AKI. It is crucial to regulate perioperative blood glucose levels, which should be managed by insulin infusion or oral antidiabetic drugs, considering their nephrotoxicity. Blood glucose levels should be maintained below 180 mg/dL during the perioperative period and closely monitored. In patients with DM, especially those at risk of AKI or CKD, caution should be taken regarding hemodynamics and aspiration risk due to autonomic dysfunction. Additionally, due to the risk of hypoglycemia in these patients, attention should be paid to the fasting period.[1,25,35]

Hypothermia affects cardiovascular, renal, neural, hematological, respiratory, basal metabolism, and hormonal systems. It has been reported that more than 40% of cases of hypothermia are associated with AKI. Intraoperative hypothermia reduces renal blood flow by causing vasoconstriction in the afferent arterioles of the kidney and triggers AKI through metabolic acidosis. It also increases the risk of perioperative AKI by slowing down the metabolism of drugs. Therefore, patients at risk for AKI, and generally all patients, should be protected from hypothermia by appropriate methods as much as possible during anesthesia.[36]

Drugs Used in Anesthesia

Anesthetic drugs are known to have cytoprotective effects by modulating the heme oxygenase-1 (HO-1) system. By activating HO-1, anesthetics prevent the development of organ damage by increasing antioxidative, anti-inflammatory, anti-apoptotic, vasoactive, and mitochondrial activity.[1,37] Inhaled anesthetics may also contribute to the development of AKI by causing Na+ and water retention due to RAAS and sympathetic nerve activation. For this reason, inhaled agents such as desflurane, isoflurane, and sevoflurane, intravenous agents like etomidate, propofol, and ketamine, dexmedetomidine opioids such as remifentanil, fentanyl, and alfentanil, and muscle relaxants including atracurium, cisatracurium, mivacurium, and rocuronium should be preferred in patients with AKI.[1,37–39] In recent years, there have been suggestions in the literature that dexmedetomidine may be preferred in AKI because it is known to increase diuresis by reducing vasopressin secretion with its sympatholytic effects, increase renal blood flow and GFR, enhance the response of renal vascular tone to vasopressors, and also have anti-inflammatory, antioxidant, and anti-apoptotic effects.[1,39,40]

Epidural anesthesia for postoperative pain control can be highly effective. It modulates spinal sympathetic outflow, increasing visceral perfusion.[1] Considering the advantages and disadvantages of general anesthesia, we believe that peripheral anesthesia blocks and epidural anesthesia methods can be used as an effective, feasible, and safe approach in

Table 3. Drugs to be used in anesthetic and pain management for patients with renal dysfunction

In patients with renal dysfunction							
Choices of anesthetic drugs				Choices of analgesic drugs			
Class of drugs	**Preferred**	**Cautious use**	**Avoid**	**Drugs**	**Patient at risk or early stage of CKD**	**Advanced CKD**	**ESKD/hemodialysis**
Induction agents	Etomidate	Thiopental propofol Midazolam ketamine	Diazepam lorazepam	Acetaminophen (PO)	325–650 mg q4 h	355–650 mg q6 h	325 mg q4–6 h
Opioids	Fentanyl remifentanil alfentanil	Morphine hydromorphone	Meperidine	Tramadol (PO)	25–50 mg q6 h	25 mg q6–8 h	25 mg q8–12 h
Muscle relaxants	Cisatracurium atracurium mivacurium	Succinyl choline vecuronium rocuronium	Pancuronium doxacurium gallamine	Morphine codeine meperidine	Reduce dose	Avoid	Avoid
Inhaled agents	Isoflurane desflurane	Sevoflurane	Methoxyflurane	Hydromorphone (PO)	1–2 mg q4 h	1 mg q4 h	0.5 mg q4 h
				Hydromorphone (SC)	0.5–1 mg q2–4 h	0.5 mg q2–4 h	0.5 mg q4 h

CKD: Chronic kidney disease; ESKD: End-stage kidney disease; PO: Oral; SC: Subcutaneous.

terms of better hemodynamic stability, pain control, and reducing the risk of postoperative AKI, especially in patients with multiple comorbidities and at risk of AKI.

Pain Management

The most critical aspect of pain management in patients at risk of AKI is multimodal analgesia, with the choice of the least nephrotoxic agents as much as possible. Acetaminophen and tramadol should be the first choice agents for pain management in patients at risk of AKI or CKD.[1,40] However, since the active metabolites of morphine, codeine, meperidine, diazepam, and ketamine are nephrotoxic, their doses should be reduced. Nevertheless, these agents should be avoided as much as possible in patients with advanced CKD and ESKD. In these patients, regional techniques are recommended, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in pain management. Drugs to be used in anesthetic and pain management in patients at risk of AKI or CKD are summarized in Table 3.[1,37–39]

Cardiac Surgery

The risk of AKI in cardiac surgery is 30–50% and is associated with a significant increase in mortality.[41] The mechanisms of AKI development in cardiac surgery are multifactorial and commonly associated with the use of cardiopulmonary pumps. These pathophysiological factors include inflammation, aortic cross-clamping time, ischemia-reperfusion injury (IRI), decreased CO, prolonged hypotension, decreased RPP, hemodilution, microembolization, coagulopathy, use of vasopressors, inotropes, and nephrotoxic drugs.[1,3,4,11,41,42] The presence of preoperative CKD in cardiac surgery is the most critical risk factor for perioperative AKI, with other important associated risk factors including age, preoperative anemia, perioperative packed red blood cell (PRBC) transfusion, CHF, emergency surgery, DM, and hemodilution (Table 2).[1–4,9,10,41,42]

Preoperative methods to prevent perioperative AKI in cardiac surgery include the use of aspirin, avoidance of nephrotoxic drugs and diuretics, maintenance of euvolemia, avoidance of anemia, use of erythropoietin, and prophylactic RRT. Intraoperative prevention methods include maintaining MAP above cerebral perfusion pressure, avoiding anemia and PRBC transfusion, choosing off-pump coronary artery bypass grafting, pulsatile perfusion during cardiopulmonary bypass (CPB), and using an intra-aortic balloon and early implementation of RRT.[1,3,4,9,10,41,42]

Transplant Surgery

Transplantation surgery is generally high-risk and complex for all patients. When AKI develops, it increases morbidity and mortality. Multifactorial risks of transplant surgery, including hemodynamic instability, IRI, and nephrotoxicity of immunosuppressive drugs, are significant risk factors that contribute to the development of perioperative AKI.[1,3,9] The incidence of associated AKI after liver transplantation

Table 4. Perioperative management for the prevention and protection of AKI

Preoperative
Patient-related factors:
• Comorbidities (obesity, CKD, DM, cardiovascular and hepatobiliary diseases, etc.)
Procedure-related factors:
• Major surgeries (extensive laparotomy, lung resections, transplantations)
• Emergency surgeries
• Cardiac surgeries
• Use of contrast-dye agents
Intraoperative
Choice of fluid solution:
• Avoid HES solutions when possible
• Balanced crystalloid solutions may prove superior to chloride-rich solutions in preventing AKI
Fluid management:
• The use of intraoperative urinary output as a guide to fluid administration may not be beneficial
• Avoid the use of diuretics unless there is a need to treat volume overload
• Implement measures during surgery to avoid blood loss and unnecessary PRBC transfusions
Hemodynamic goals:
• Avoid a low MAP, even for relatively short periods
• Current evidence does not recommend the use of one vasopressor over another
• Low-dose dopamine is no longer considered "renoprotective" and is not recommended
• The first choice inotrope is norepinephrine
General considerations:
• Avoid the use of aminoglycosides unless there is no suitable, less nephrotoxic alternative available
• Utilize new biomarkers

AKI: Acute kidney injury; CKD: Chronic kidney disease; DM: Diabetes mellitus; HES: Hydroxyethyl starch; UO: Urinary output; PRBC: Packed red blood cell; MAP: Mean arterial pressure.

ranges from 14% to 78%, with 17% requiring RRT. Strategies to prevent the development of AKI after liver transplantation include maintaining hemodynamic stability, using terlipressin, and avoiding or reducing high doses of immunosuppressive agents, especially tacrolimus, after surgery.[1,9,43]

Perioperative Management

The main goal of preventing and treating AKI is to identify patients with risk factors before surgery and optimize them as much as possible. Perioperative management and recommendations for preventing and protecting against AKI are summarized in Table 4. Some important points to consider in anesthesia management include.[1,3,4,9]

Hemodynamic Monitoring and Targets

The primary goal in the perioperative period should be to ensure adequate perfusion and oxygenation to the tissues and to prevent organ damage.[1] Regardless of the type of surgery, a standard monitoring method should be applied. In addition to standard monitoring, it is essential to closely monitor blood pressure control, fluid-electrolyte, and acid-base balance by performing arterial cannulation when necessary. Knowing the amount of fluid withdrawn, serum creatinine (sCr), electrolytes, acid-base status, and state of consciousness in preoperative patients undergoing RRT is vital.[1,8,13] If effective RRT has not been performed, the patient should not undergo surgery without optimizing it, and if necessary, RRT should be repeated, and the patient should be considered for surgery under the most appropriate conditions. However, in patients at risk, mechanical ventilation parameters should be adjusted appropriately for the patient, and care should be taken as excessive pressures will disrupt venous return and RPP.[1,8,13,15,25,30]

To prevent AKI in the perioperative period, it is recommended that MAP be maintained above 65–70 mmHg (above 75 mmHg in patients with chronic hypertension).[27] The duration of hypotension that develops in the perioperative period is significant. It should be kept in mind that even short periods of hypotension contribute to the development of AKI in patients with advanced age and multiple comorbidities. It is crucial to monitor the patient closely depending on the size and urgency of the surgery and to apply the appropriate monitoring method, from non-invasive to invasive, to prevent organ damage.[27–30]

Choose a Fluid

The primary purpose of fluid therapy in the intraoperative period should be to preserve intravascular volume and ensure adequate tissue oxygenation and perfusion. Maintaining proper fluid balance during anesthesia is highly important and should be a critical perioperative hemodynamic goal to correct hypovolemia and avoid AKI.[1,3,4,13,15,30] Both hypervolemia and hypovolemia are essential factors that trigger AKI and are associated with increased mortality and morbidity. Hypervolemia causes Na^+ and water retention, reduces renal blood flow, and contributes to the development of AKI by causing renal interstitial edema, and organ dysfunctions may develop along with tissue and organ edema. Hypovolemia causes hypotension, tissue hypoxia, and then organ dysfunction. In response to the resulting hypovolemia, there is activation of RAAS, which causes angiotensin II activation and ADH release, leading to vasoconstriction in afferent arterioles and a decrease in GFR, which reduces renal blood flow and therefore contributes to the development of AKI.[1,13,15,25,30,44,45]

Ensuring adequate intravascular volume in the patient, especially in major surgeries, is crucial. The choice of fluid should be determined according to the patient's risks, existing comorbidities, and the benefit-harm ratio.[44] Crystalloid solutions such as balanced solutions (Ringer lactate, Plasma-Lyte, etc.) or normal saline (0.9%) are frequently used in fluid therapy. Colloid solutions are often used for albumin, fresh frozen plasma, synthetic hydroxyethyl starches (HES), and gelatins. Electrolyte, pH, and osmolarity levels vary widely in crystalloid solutions. Crystalloid administration may not accurately reflect intraoperative oliguria, fluid status, or risk of developing AKI due to decreased clearance and slow distribution during anesthesia. Saline, unlike balanced crystalloids that more closely resemble plasma content, contains only NaCl, which can cause hyperchloremia and contribute to the development of AKI by causing vasoconstriction in afferent arterioles, reducing glomerular blood flow, and inducing metabolic acidosis. Currently, it is recommended to avoid perioperative and intraoperative use of colloid solutions in patients with AKI and those at risk of AKI.[1,13,25,44,45] If there is no K^+ problem, it is best to administer a balanced crystalloid, and we generally prefer Isolyte S (pH: 7.4, osmolarity: 295 mOsmol/L concentrations of electrolytes (mEq/L) (Na^+ 141, K^+ 5, Mg^{++} 3, Cl^-98; HPO^-4 - 1; acetate 27, gluconate 23), considering the K+ and Cl- levels. In hypovolemia, balanced fluid and vasopressor should be administered, and in hypervolemia, fluid restriction, loop diuretics, and early RRT should be considered. Since inappropriate and unnecessary use of diuretics may cause nephrotoxicity in patients at risk of AKI, they should be used only for the treatment of hypervolemia.[1,13,25,44,45]

Use of Inotropes and Vasopressors in Acute Kidney Injury

The most crucial benefit of using vasopressors to prevent AKI is increasing MAP and keeping RPP within autoregulation limits. However, the vasoconstriction in renal vascular tone and related side effects often lead to the avoidance of these drugs. Norepinephrine causes vasoconstriction of renal arterioles, reducing renal blood flow but not GFR. However, it is primarily the safest and most effective vasopressor used in clinics.[46] In recent years, vasopressin and angiotensin II have begun to be used to increase renal blood flow, showing a renal protective effect, especially in sepsis-related AKI. Epinephrine is used less frequently, mainly due to its potential to cause tachycardia, lactatemia, and hyperglycemia, owing to a pronounced α-adrenoreceptor effect. Low doses of dopamine may increase UO for years due to its diuretic effect, but in recent years, it is no longer used as a kidney protector and is not recommended for treating AKI.[1,25,46,47]

Early Diagnosis and New Biomarkers

The most commonly used parameters to diagnose and classify AKI in the perioperative period are based on increased sCr concentrations and decreased UO. Due to the long half-life of sCr and the renal reserve capacity that can be utilized before baseline GFR begins to decline, sCr takes time to reflect GFR, resulting in a delayed accurate recognition of AKI. Since UO may not change during AKI and the increase in sCr usually occurs later (48–72 hours), the increase in sCr can be easily affected by fluid overload, drugs such as steroids, nutrition, and conditions such as muscle trauma.[1,3,4,48,49]

Although sCr is frequently used to diagnose AKI in the perioperative period, it is a biomarker with low sensitivity and specificity that provides limited information about acute changes in renal function. An increase in sCr concentration is not observed until there is approximately a 50% loss of kidney function.[1,3,4,25,48,49]

Cells in the kidney produce important damage biomarkers that detect damage to the kidney early before clinical signs of AKI appear. These biomarkers are critical and valuable as they directly relate to underlying localized kidney damage, contributing to a much earlier and more accurate diagnosis of AKI.[48] These

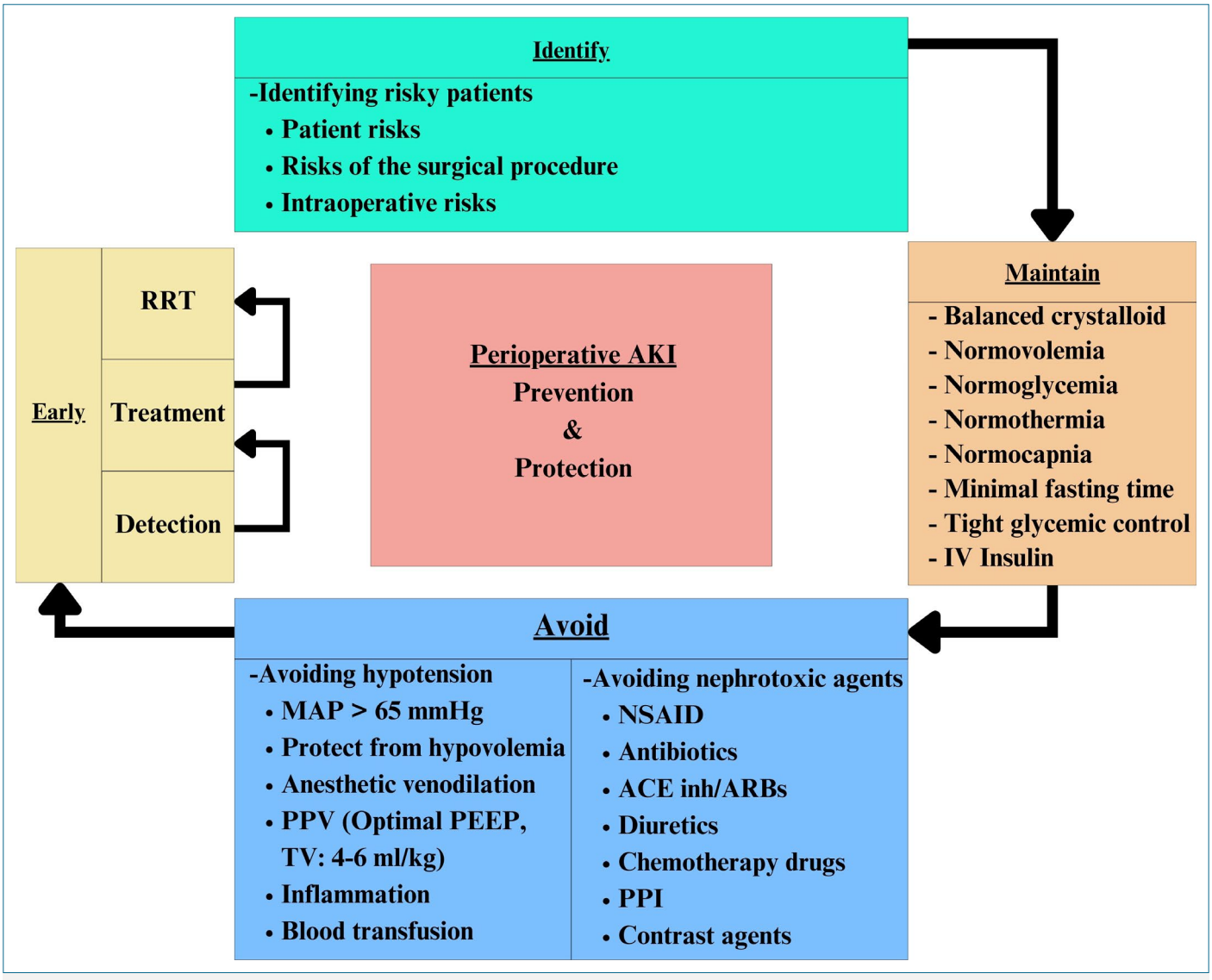

Figure 3. Critical recommendations for AKI.

AKI: Acute kidney injury; IV: Intravenous; MAP: Mean arterial pressure; PPV: Positive pressure ventilation; PEEP: Positive end-expiratory pressure; TV: Tidal volume; NSAIDs: Nonsteroidal anti-inflammatory drugs; ACEinh: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin-II receptor blockers; PPIs: Proton pump inhibitors.

biomarkers can indicate different types of kidney damage depending on the internal and external locations of the kidney. New early markers of AKI are needed to enhance prevention, detection, diagnosis, treatment, and prognosis prediction of AKI. Some promising biomarkers include neutrophil gelatinase-associated lipocalin, cystatin C, interleukin 18, kidney injury molecule-1, insulin-like growth factor-2, tissue inhibitor metalloproteinase-2, insulin-like growth factor-binding protein 7, microalbumin, and liver fatty acid-binding protein.[48,49] Critical recommendations for preventing and protecting against AKI are summarized in Figure 3.[1,3,9–11]

CONCLUSION

Perioperative AKI continues to be a challenging issue for the anesthesiologist and surgeon and is the most common, heterogeneous, and severe complication in the perioperative period. Perioperative AKI is associated with increased morbidity, mortality, prolonged hospital stays, elevated costs, and greater healthcare resource utilization. An accurate and better understanding of the risk factors that contribute to the development of perioperative AKI may facilitate early diagnosis, prevention, and management of AKI. The pathophysiology of

perioperative AKI is quite complex and includes a combination of hemodynamic instability, microcirculation disruption, endothelial dysfunction, inflammation, and tubular cell damage. Early identification and prevention of risk factors of perioperative AKI and optimization of the patient are the most critical steps. Appropriate anesthesia management during the intraoperative period is essential to prevent AKI. The main goals of this management should be to ensure hemodynamic stability (MAP >65 mmHg), adequate intravascular volume and CO, effective tissue and organ perfusion and oxygenation, appropriate monitoring, application of the correct fluids, anesthesia, pain control, mechanical ventilation method, avoiding nephrotoxic drugs, contrast dyes, and unnecessary blood transfusions, and early RRT. New biomarkers should be used to rapidly detect, intervene, and treat AKI. For patients with multiple comorbidities, comprehensive preoperative preparation of the patient using a multidisciplinary approach, optimization, correct collaboration with the anesthesiologist, nephrologist, and surgical team, and close postoperative follow-up are essential in preventing AKI and other complications.

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