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REVIEW ARTICLE

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The impact of perioperative acute kidney injury/failure on short and long surgical outcomes

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Abstract

The development of acute kidney injury after surgery is associated with significant mortality and morbidity and with worse short and long-term outcomes. Patients who develop acute kidney injury are at an increased risk of developing long-term renal dysfunction, which leads to lower quality of life and greater financial burden on the healthcare system. Although there are various systems to classify the severity of acute kidney injury, most systems only measure components that deteriorate after significant renal damage, such as urine output and serum creatinine. Surgical trauma and stress trigger acute kidney injury development, in addition to multiple co-morbidities, cardiovascular disease, and postoperative factors. The pathophysiology of acute kidney injury is complex, and this is reflected in the heterogenous population that is affected. Treatment is largely supportive and focuses on ensuring adequate renal perfusion, correcting electrolyte abnormalities and avoiding further renal injury. Current research focuses on novel biomarkers that detect decreased renal function earlier and that the deteriorating renal function can be treated before long-lasting damage occurs. This review discusses the epidemiology, aetiology, risk factors, and short and long-term surgical outcomes of acute kidney injury. Treatment, prevention, and recent developments in future research are also discussed.

Keywords Acute kidney injury, Surgical outcomes, Perioperative, Morbidity; Mortality

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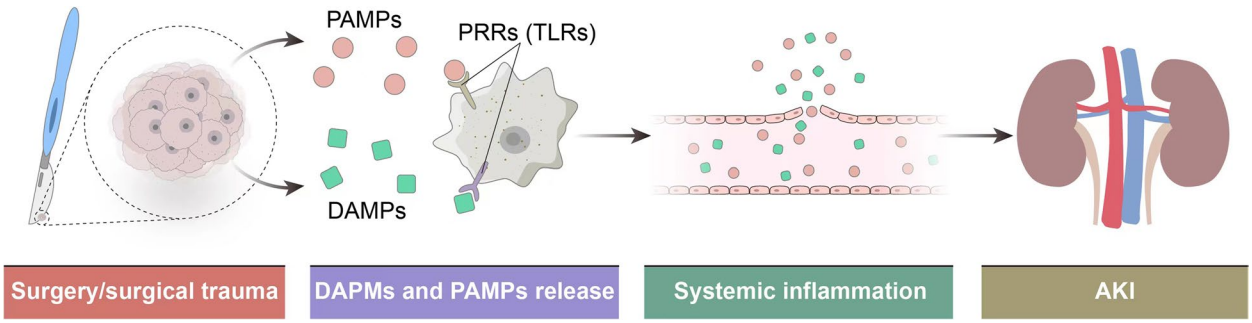
Graphical Abstract



1 Introduction

Perioperative acute kidney injury (AKI) accounts for 18–47% of all hospital-associated AKIs occurring after surgery [1]. Surgical patients with comorbidities are at greater risk of developing renal dysfunction [2]. AKI represents a large burden of disease on the healthcare system in terms of mortality and cost [3]. Importantly, transient perioperative deterioration in renal function can lead to devastating outcomes such as long-term renal dysfunction [4–6]. Developing preventive strategies to tackle the occurrence of perioperative AKI is urgently needed, as once AKI has occurred, treatment is currently largely supportive [7]. This review was completed using a systematic approach, with predetermined inclusion and exclusion criteria. The databases EMBASE and Medline were searched extensively for relevant papers published in English up to 2021. The search terms "perioperative" and "acute kidney injury" or "acute kidney failure" were combined with each of the following terms: "surgical outcomes", "mortality", "morbidity", and "management". Here, we summarised the literature mainly published in the past 10 years or so and provide a critical insight into the understanding of AKI and of short and long term surgical outcomes. This review gives an overview of the pathophysiology, treatment, and outcomes of perioperative AKI, and discusses the current updates of AKI prevention and management.

2 Renal physiology

The kidneys receive 20–25% of the cardiac output [8, 9], the highest percentage of cardiac output per gram of tissue [10]. Blood flow is maintained primarily by the vascular tone of the afferent arteriole in response to tubuloglomerular feedback of changes in sodium chloride (NaCl) concentration in the tubular fluid [11]. The nephron is divided structurally and functionally into segments: the glomerulus, proximal tubule, loop of Henle, distal tubule and collecting tubule system. The schematic illustration of tubular structure and functions, and the mechanism of action of the classes of diuretics is presented in Fig. 1.

3 Acute kidney injury

The definition of diagnosis criteria of AKI is debatable. The Acute Dialysis Quality Initiative group devised the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria for the diagnosis and classification of impaired kidney function (Table 1) [12].

The Acute Kidney Injury Network (AKIN) then modified the RIFLE criteria by adding changes in serum creatinine when they occur within a 48-h period [13]. More recently, in 2012, Kidney Disease: Improving Global Outcomes (KDIGO), a non-profit foundation, published guidance that covered both the RIFLE and AKIN criteria [14]. They proposed three stages of AKI (Table 2) and defined AKI as any of the following:

- A rise in serum creatinine (SCr) by 0.3 mg/dl (26.5 μmol/l) within 48 h;
- A rise in SCr to 1.5 times of the baseline, which is known or presumed to have occurred within the prior seven days;
- Urine volume < 0.5 ml/kg/hour for six consecutive hours

The RIFLE, AKIN and KDIGO criteria are currently the most widely accepted definitions of AKI. However, there is no agreement as to which provides the most accurate estimation of incidence or mortality.

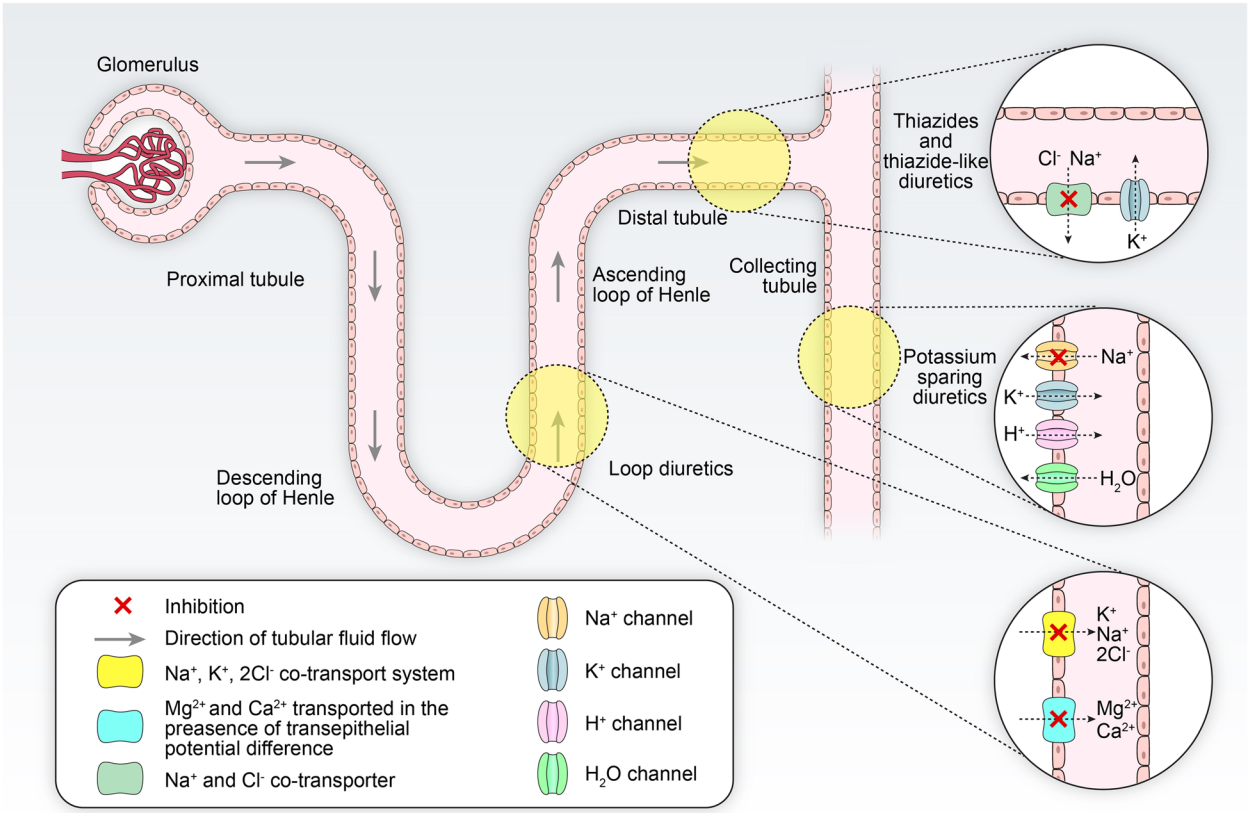


Fig. 1 Schematic illustration of renal tubular structure and functions, and the site and action of classes of diuretics

Table 1 Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [12]

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* Baseline SCr ≥ 4 mg/dL with acute rise of SCr > 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		

GFR Glomerular filtration rate, *SCr* Serum creatinine

4 Epidemiology

AKI incidence can reach 30% in cardiac surgery patients [15] and in other types of major surgery, with a lower rate in elective procedures compared to emergency procedures [16]. However, a rate of only 1% of general surgery procedures resulted in AKI was also reported [2]. The discrepancies in different studies may be caused by heterogenous populations and different AKI classification systems. AKI epidemiology also differs in low or middle-income countries (LMICs) versus high-income countries (HICs) [17]. Although community-acquired AKI is more common in LMICs, perioperative AKIs occur more often in cardiac surgery procedures and in children undergoing non-cardiac surgery in HICs [18].

Table 2 Kidney Disease: Improving Global Outcomes (KDIGO) stages of AKI [14]

Stage	Serum creatinine	Urine output
1	1.5 to 1.9 times baseline *or* ≥ 0.3 mg/dl increase	< 0.5 ml/kg/hour for 6 to 12 h
2	2.0 to 2.9 times baseline	< 0.5 ml/kg/hour for ≥ 12 h
3	3.0 times baseline *or* Increase in serum creatinine to ≥ 4.0 mg/dl *or* Initiation of renal replacement therapy *or* in patients < 18 years a decrease in eGFR to < 35 ml/minute per 1.73 m^2	< 0.3 ml/kg/hour for ≥ 24 h *or* anuria for ≥ 12 h

5 Aetiology of AKI

The aetiology of AKI can be classified into pre-renal, intrinsic and post-renal depending on the cause.

5.1 Pre-renal

Pre-renal AKI refers to a decreased glomerular filtration rate (GFR) due to renal hypoperfusion. Kidneys are heavily reliant on adequate blood supply, and even a small reduction in perfusion can have a profound effect on the GFR. Common causes include hypovolaemia, impaired cardiac function, systemic vasodilation and increased vascular resistance [9]. If the pre-renal cause can be reversed promptly, renal function can generally be restored.

5.2 Intrinsic

Intrinsic AKI develops following damage to the glomeruli, tubules, interstitium or intra-renal blood vessels [9]. Most commonly, the tubules are damaged, and this is referred to as acute tubular necrosis. Acute glomerulonephritis can lead to glomerular damage, and vascular damage reduces perfusion and consequently GFR. Acute interstitial necrosis is caused by infection or as a reaction to a wide range of medications.

5.3 Post-renal

Post-renal AKI is caused by increased intratubular pressure due to acute obstruction of urinary flow [8]. The raised pressure combined with impaired renal blood flow and inflammation leads to a decreased GFR [9, 19]. Post-renal AKI can be further divided into intrarenal and extrarenal depending on the site of obstruction. Intrarenal causes include nephrolithiasis, papillary necrosis and thrombi, whereas prostatic hypertrophy; bladder, prostate or cervical cancer; retroperitoneal fibrosis and improperly placed catheters cause extrarenal obstruction [9]. As with pre-renal causes of AKI, prompt reversal of the obstruction usually leads to a quick return of function.

6 Common processes involved in AKI

Under physiological conditions, permeability, vascular tone, coagulation and inflammation are regulated by endothelial cells [20]. If they become damaged primarily because of hypoxia, ischaemia or nephrotoxicity, these processes can be compromised, and renal function will be impaired. Most AKI cases involve multiple different pathophysiological processes provoked by a triggering event [12, 20].

6.1 Ischaemia

Systemic hypotension can cause endothelial cell injury and subsequent local release of endothelin, angiotensin II and catecholamines, which leads to vasoconstriction and may worsen ischaemia [20, 21]. When ischaemic tissue is reperfused, rapid production of reactive oxygen species (ROS) can activate the opening of the mitochondrial permeability transition pore, resulting in depolarisation of mitochondria, which decreases adenosine triphosphate (ATP) synthesis and increases ROS production [22, 23]. ATP depletion causes cytoskeleton changes to epithelial and endothelial cells, impairing function [24]. Death of tubular cells reduces overall function, and results in a clogged tubule and loss of pressure gradient, further reducing the GFR [22, 23].

Ischaemia can cause cell necrotic and apoptotic death [24]. Prolonged ischaemia (45 min) tends to cause necrotic cell death, whereas apoptosis follows shorter ischaemia times (30 min) [22]. Renal necrosis is genetically driven whereby the rapid disintegration of the plasma membrane leads to damage-associated molecular patterns escaping the cell, resulting in a striking inflammatory response in the tissue, and organ injury or failure [22, 24]. In apoptosis, controlled digestion of cells with intact plasma membranes reduces the inflammatory response and limits tissue damage [24]. It is therefore critical that ischaemic episodes are minimised to prevent more extensive damage occurring to the tissue.

6.2 Hypoxia

Renal hypoxia occurs when there is a mismatch between renal oxygen supply and demand. Insufficient oxygen supply can be caused by anaemia or reduced flow through peritubular capillaries [25]. Increased renal oxygen demand has been shown to occur in hypertensive and diabetes mellitus models [26, 27]. Susceptibility

varies throughout the tubule, with the thick ascending limb and collecting duct of the medulla being at greatest risk of hypoxia [28]. Intraoperatively, simultaneous alterations in renal vasoreactivity and perfusion pressure can lead to regional hypoxia. Damage and reduced filtration impair the ability to remove inflammatory mediators and leads to inflammatory responses in which cells adhere to the peritubular capillary endothelium, causing medullary congestion and reduction in oxygen delivery [22, 23, 29].

6.3 Nephrotoxicity

Up to 60% of cases of in-hospital AKI may be drug-induced [30]. Non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACE-Is), aminoglycoside antibiotics and intravenous imaging contrast agents, among many other medications, are known to be nephrotoxic.

Chronic use of NSAIDs can impair autoregulation of renal blood flow [31]. NSAIDs act through cyclooxygenase (COX) enzyme inhibition, limiting the conversion of arachidonic acid to prostaglandins, prostacyclins and thromboxanes [31, 32]. Prostaglandins increase renal perfusion through vasodilation, and so NSAID use can lead to reduced renal perfusion and a decreased GFR. Despite this, preoperative low-dose aspirin may be associated with a lower incidence of renal impairment in cardiac surgery [33].

ACE-Is inhibit the production of angiotensin II, a vasoconstrictor formed from angiotensin I by ACE, that constricts both the afferent and efferent arterioles [34]. In patients whose glomerular filtration is solely dependent on angiotensin II-mediated efferent vascular tone, for example in heart failure or severe volume depletion, ACE-Is can provoke AKI [35]. However, this vasodilatory effect is well known to be renoprotective in chronic kidney disease and diabetic nephropathy [36].

Antibiotics are commonly used perioperatively, and some studies suggest the incidence of antibiotic-induced AKI may be as high as 18–36% [37, 38]. One study found that aminoglycosides, beta-lactam antibiotics, vancomycin and amphotericin B were responsible for most cases of antibiotic-induced AKI [37]. Aminoglycosides accumulate in tubular cells and inhibit lysosomal enzymes, leading to the formation of membrane fragments and myelin bodies [39]. The nephrotoxic mechanism of vancomycin, a glycopeptide antibiotic, is thought to include oxidative stress, inflammatory injury from complement activation and mitochondrial damage, and causation of obstructive tubular casts [40, 41].

The possible nephrotoxicity of anaesthetics was reported. For example, methoxyflurane was used in the old days and found to cause dose-dependent nephrotoxicity due to its metabolites, which primarily consist of dichloroacetic acid and fluoride; it is not clear if fluoride, or its combination with dichloroacetic acid, drives the nephrotoxicity [42, 43]. This finding led to its decline as an anaesthetic agent, although it is currently used for analgesia at lower doses in some countries [42]. Of the commonly used inhaled anaesthetics today, sevoflurane is metabolised at a greater rate than isoflurane or desflurane, but lower than methoxyflurane. Historically, there have been fears surrounding sevoflurane's possible nephrotoxicity. Sevoflurane's metabolites include hexofluoroisopropanol, compound A, and fluoride, and high fluoride concentrations are similar to methoxyflurane metabolites that have been linked to nephrotoxicity [44]. However, the same effect has not been seen with sevoflurane, possibly due to differences in the other metabolites or the site of fluoride metabolism, which is mainly intrarenal for methoxyflurane but hepatic for sevoflurane [45]. Clinical studies have not found greater renal dysfunction with sevoflurane compared to other inhaled agents, even when it reached a higher peak plasma fluoride [42, 46]. Therefore, it is worth considering not using sevoflurane in patients at high risk of kidney dysfunction.

7 Risk factors

Acute kidney injury often occurs after major surgery, including abdominal, cardiac, respiratory, and neurosurgery procedures. Most studies focus on AKI after cardiac surgery and cardiopulmonary bypass (CPB) [47–49]. AKI has also been associated with liver transplantation, gastric bypass surgery, and gastrointestinal complications following surgery [50–52].

7.1 Preoperative factors

There is little analysis into how much preoperative factors predisposes a patient to developing AKI in comparison to other risk factors. Patients that developed AKI were older, more likely to be male, had existing cardiovascular risk factors, previous myocardial infarctions or strokes, higher pulmonary arterial pressure in preoperative echocardiography, lower haemoglobin before surgery, and pre-existing renal impairment [4, 5, 49, 53]. Given these known risk factors, identifying high risk patients pre-operatively and optimising their renal function pre- and post-operatively is very important for elective surgery. Interestingly, one study found that patients who had pre-existing chronic kidney disease (CKD) and developed AKI after surgery had a lower in-hospital mortality rate but a higher morbidity rate despite being older and having more comorbidities, possibly because of extra precautions and earlier nephrology consultations [54]. However, a greater proportion of patients with pre-existing CKD required dialysis at discharge.

7.2 Intraoperative factors

Patients that underwent emergency surgery (versus elective surgery) had a greater volume of blood loss and fluid transfusion during surgery, more re-exploration surgery, more complex procedures (such as combined valve replacement and coronary artery bypass graft (CABG)), longer surgery duration, and spent more time on CPB were at greater risk of developing AKI [5, 50, 53]. Patients who underwent cardiac surgery were more likely to develop AKI compared to other major procedures [50]. In a retrospective cohort study, 145/843 cardiac surgical patients who underwent CPB had a > 25% increase in their baseline serum creatinine in the first week postoperatively, with > 75% developing renal deterioration in the first two days [4]. However, long-term mortality was higher for non-cardiothoracic surgery procedures (oesophageal, intestinal, and liver surgery), especially if they developed AKI requiring dialysis [55].

7.3 Postoperative factors

Postoperative factors can be modified to avoid AKI development in vulnerable patients and minimise subsequent long-term renal damage. Negative factors include a higher level of creatinine postoperatively and at discharge, greater need for a postoperative intra-aortic balloon pump, postoperative low output syndrome, longer course of vasoactive drugs, and a higher arterial lactate 24 h after admission [4, 5].

8 Impact on short-term surgical outcomes

Depending on surgical type, surgical procedure and patient population, up to 47% of surgical cases are complicated by AKI [2, 56–59]. The risk of post-operative hospital mortality is higher in patients with AKI than in those without. Importantly, mortality remains higher in patients with perioperative AKI even after complete renal function recovery [3, 60].

8.1 Cardiac surgery

AKI incidence is greater in cardiac surgery than in other specialties [15, 57, 61–65]. Indeed, it was reported that 75% of patients undergoing CPB developed renal deterioration in the first 2 days post-operatively [4]. Furthermore, another study found that AKI occurred in 71.7% of the cases within 72 h post-cardiac surgery; 30-day all-cause mortality was 4.4%, and 5.6% had persistent renal dysfunction (PRD), and by day 30 after surgery, a major adverse kidney event (defined as a combination of mortality, PRD and the need for renal replacement therapy) had occurred in 10% of patients [66]. 30-day mortality in patients with perioperative AKI who underwent cardiac surgery was 3.5–5 times higher than in those without AKI. A meta-analysis of postoperative AKI in patients with Type A acute aortic dissection found that AKI was associated with a 249% increase in 30-day mortality [66]. Another study found that 30-day mortality in patients who developed AKI following transcatheter aortic valve replacement was 29%, four times higher than in controls [67].

8.2 Other surgeries

In patients who underwent open and laparoscopic abdominal surgery between 2007 and 2014 at a centre in Iceland, 6.8% of cases were complicated with AKI; patients with AKI had a 30-day mortality 3.4 times greater than controls (18.2% vs 5.3%) [68]. Generally, AKI occurs in 1–11.8% of patients undergoing general surgery procedures; although fewer than estimates for cardiac surgery, the mortality may be higher [2, 68–71]. One study of patients undergoing intra-abdominal surgery found a 30-day mortality as high as 31% in patients with AKI compared to 1.9% in those without [72]. Another study reported a mortality rate 12.7 times greater in those with AKI than non-AKI patients undergoing gastric surgery [73]. However, several other studies describing mortality rates between 6–9 times higher in cases with AKI [2, 69, 71, 74, 75]. Studies looking at AKI following hepatic resection reported an incidence between 4.3–15.1%, with a 30-day or hospital mortality between 14.1–23.2% for those with AKI compared to 0.8–2.3% in those without [76–78]. One study also found that the rate of AKI increased significantly from 4.3% to 18.2% in patients with raised preoperative creatinine. A broader study of hepatobiliary surgeries found a similar incidence of 7.6% but slightly lower mortality: 7.1% with AKI versus 2.5% non-AKI [79].

9 Impact on long-term surgical outcomes

9.1 Morbidity and mortality

Both the occurrence of AKI and its severity are independently predictive for worse long-term mortality at 1 year and long-term, and even small transient increases in SCr postoperatively have a significant negative impact on long-term survival [4–6]. In a retrospective study involving 2840 patients, those with AKI post-cardiac surgery and CPB had worse mortality at a mean follow-up of 6.9 years than those who didn't have AKI (21.4% vs 10.6%) [24]. Survival at one year was 88% for RIFLE class Risk, 55% for RIFLE class Injury, and 39% for RIFLE class Failure, demonstrating that the degree of renal function deterioration was dependent on initial AKI severity. The mortality differences associated with the occurrence of AKI and its severity also persist over time [80].

Patients who developed AKI requiring dialysis (AKI-D) had an adjusted hazard ratio of 3.22 for all-cause long-term mortality compared to controls in a study of 8320

surgical patients at a median follow-up of 294.5 days [55]. In a retrospective study of patients who had undergone major surgery, the 6-month mortality rate of AKI patients was almost 4 times higher than patients who did not develop AKI [24]. The patients with AKI that died at 6 months had higher Simplified Acute Physiology Score (SAPS) II, Acute Physiology And Chronic Health Evaluation (APACHE) II, and American Society of Anesthesiologists Physical Status (ASA-PS) scores, indicating a greater severity of disease before discharge. AKI after cardiac surgery also resulted in a greater likelihood of further hospitalisation due to cardiovascular events such as stroke and myocardial infarction, and increased the risk of long-term heart failure and death [6, 81].

9.2 Renal function

Despite complete recovery of renal function, patients that developed perioperative AKI had much lower survival rates at 1 and 2 years after surgery than patients who did not develop AKI. Long-term mortality also depends on the use of renal replacement therapy (RRT). In a retrospective study of 1294 patients that required acute dialysis after major elective surgery, 27.2% of patients required chronic dialysis beyond hospital discharge [82]. Initial AKI severity also played a role: in a study involving 29,330 patients, 5.2% of patients who developed postoperative AKI AKIN stage 2 or 3 after a CABG procedure developed end-stage renal disease (ESRD) and required renal replacement therapy, but only 1.6% of AKIN stage 1 patients developed ESRD [6]. The risk of developing ESRD after CABG was independent from preoperative renal function.

The form of RRT given also influences long-term renal impairment. The main indications for RRT initiation are if the patient develops severe metabolic acidosis, life-threatening hyperkalaemia, or refractory fluid overload, but the decision is ultimately clinical [83]. Continuous renal replacement therapy (CRRT) has traditionally been used in patients who are critically ill and have some degree of haemodynamic instability [84]. In patients who received CCRT after developing perioperative acute renal failure after CPB, long-term RRT was rarely needed [50]. CRRT produced similarly promising results in preserving renal function even when patients had elevated preoperative SCr levels or renal impairment. Patients who received CRRT acutely after surgery had a very low risk of requiring long-term RRT and had a lower mortality rate compared to patients that received intermittent RRT [50]. Of the 92/3172 patients that received CRRT after cardiac surgery, only 2 patients required ongoing renal replacement therapy long-term.

Although postoperative AKI is common following major surgery, many patients achieve renal recovery. In a multicentre prospective observational study of patients requiring RRT after postoperative AKI, 84.7% of the 137 patients who survived 90 days achieved renal function recovery and no longer required RRT [85]. Patients who achieved complete renal recovery had much better mortality rates than patients who had incomplete renal recovery even if they did not require renal support. In a prospective study, patients with incomplete renal recovery, defined as SCr > 44 μmol/L above baseline at discharge, had a risk rate of 2-year death of 8.64, compared to those who achieved complete renal recovery with a risk rate of 1.79 [80]. Both the initial AKI severity and extent of renal recovery were independent risk factors for long-term survival [80, 86].

Postoperative AKI also increases the risk of developing postoperative CKD, with greater risk associated with increasing AKI severity at diagnosis [80, 87]. Similar to mortality trends, the increased risk of developing CKD after AKI persisted even after complete renal function recovery, and patients with incomplete renal recovery had a greater relative risk for CKD progression (15.05 vs 1.92) [80]. CKD was also a risk factor for cardiovascular events and postoperative mortality [88, 89].

9.3 Multiple organ failure

Uraemia, fluid overload and electrolyte imbalances are well known consequences of AKI that can cause distant organ damage. It is also thought that released pro-inflammatory cytokines are associated with AKI may contribute to this via a systemic response [90]. The interaction between the kidneys and heart is well-established as cardiorenal syndrome, specifically type 3 [91], whereby multiple processes contributed to acute cardiac dysfunction including changes to contractility and arrhythmia caused by uraemia and hyperkalaemia, respectively [92, 93]. Uraemia is also known to cause neurological complications ranging from irritation and cognitive impairment to seizures and death, more commonly in AKI than CKD [94], as well as a high incidence of dementia in patients with renal failure [95].

9.4 Quality of life

Long-term renal replacement therapy and end-stage kidney disease negatively impacts a patient's quality of life [96]. However, there have been few studies examining the quality of life in individuals after they recover kidney function and do not require ongoing RRT. In one retrospective study of 1200 patients who underwent major surgery, they were evaluated 6 months after discharge using the 36-Item Short Form Survey (SF-36), and on their level of dependency using Activities of Daily Living (ADL) [24, 97]. Postoperative AKI patients had worse SF-36 scores and were more dependent in instrumental

ADL (I-ADL) such as cleaning, cooking, and taking public transportation, although they were comparable to non-AKI patients in Personal ADL (P-ADL) [24]. At 6 months follow-up, patients were more dependent on many ADL domains, with 78% of patients dependent in at least one I-ADL activity, marking a clear deterioration from before surgery.

9.5 Financial burden

As well as increased mortality, AKI also poses a financial burden. A single-centre study looked at over 50,000 cases of AKI in the US over an 18-year period [3]. They found that patients with any AKI had hospital costs that were 159% of the costs for patients without AKI ($42,600 vs $26,700). Similarly, another study identified over 1 million patients who underwent a CABG, valve replacement surgery, or both between 2008–2011 and found the average hospitalisation cost for patients who developed AKI was twice the average cost for patients who did not develop AKI ($77,178 vs $38,820) [59]. One study also found all costs were doubled for patients with AKI [57].

10 Prevention and treatment

10.1 Early AKI detection

10.1.1 Biomarkers

Traditionally, functional markers such as SCr and urine output are used to diagnose AKI, and their levels define AKI staging criteria. However, since changes in these markers demonstrate a functional renal change, they cannot be detected until after a significant decline in renal function has already occurred. In a retrospective cohort study of 3862 thoracic surgery patients, 205 developed postoperative AKI [98]. Although intraoperative oliguria was moderately associated with postoperative AKI (adjusted odd ratio 2.60), it had poor predictive ability with a sensitivity of 5.9%. To aid the early detection and treatment optimisation in patients at risk of AKI, several studies reported the use of novel biomarkers to detect subclinical renal impairment in the form of tubular injury [99].

The serum and urine neutrophil gelatinase-associated lipocalin (NGAL) biomarker has been particularly effective at predicting AKI where the renal insult is well-defined, such as after cardiac surgery. In animal models, NGAL is one of the earliest up-regulated biomarkers after renal tubular ischemic injury [100]. In a 2010 prospective observational study, plasma NGAL (pNGAL) was effective at predicting AKI onset within 48 h in a heterogenous adult ICU population [101]; pNGAL was also consistently higher in AKI patients than controls, and the levels increased with greater AKI severity. The marker may also be useful in predicting renal recovery and future independence from RRT [102]. Although pNGAL is highly sensitive for renal injury, it is non-specific for AKI [103]. However, its ability to predict AKI in a population with mixed comorbidities and risk factors makes it a promising biomarker for future clinical practice [104–107]. Other biomarkers that are being explored include urinary markers such as liver-type fatty-acid-binding protein (L-FABP), kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and interleukin 18 (IL-18); these may also play a role in the early detection of AKI in specific patient populations [108–111]. Recent observational cohort studies in cardiac surgery patients have explored markers such as intraoperative venous congestion, defined as elevated central venous pressure, which was associated with an increased probability of postoperative AKI and greater severity of AKI [112]. A single-centre study of 35,337 patients found that increased preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration was correlated with greater any-stage AKI, and significantly improved AKI prediction [113].

Some biomarkers have been criticised for not being sensitive or specific enough. Urine IL-18, whilst an early predictive marker of AKI severity and mortality, is also elevated in endotoxemia and cisplatin toxicity [114], and KIM-1 is increased in response to nephrotoxins, but also in tubulointerstitial inflammation and fibrosis [115]. Although NGAL is a highly specific and sensitive marker in predicting AKI in children two hours after CPB being reported [116], another study found serum NGAL to be non-specific when measured in critically ill children with septic shock [103]. Researchers have tried to mitigate this by combining various biomarkers to optimise both the sensitivity and specificity of early AKI prediction [24, 104, 105]. In a retrospective study, combining functional and tubular biomarkers was shown to be superior to functional markers alone in predicting AKI severity and duration; they also proposed that the combination could also provide insight into the pathophysiology of the AKI, which could allow for a more accurate prediction of recovery or prognosis [104].

10.1.2 Nephrology consultation

Criteria for in-hospital nephrology consultation in AKI patients is not standardised. Multiple studies have shown that earlier nephrology consultation (within two days) may lead to better functional outcomes [117], and among patients who received a nephrology consultation, a delayed consultation led to worse mortality [118]. Despite the lack of standardised criteria guiding nephrology consultations, certain characteristics linking AKI severity to timing of nephrology consultation can be observed: in one observational study of AKI patients in ICU, 52% of patients were seen by a renal consultant, and those that

were seen had worse AKI severity, higher creatinine levels, lower urine output, and longer ICU stays [118]. In a prospective observational cohort study, patients with existing CKD who developed AKI had a quicker nephrology consultation than patients without CKD, and this may have contributed to their lower in-hospital mortality [54]. Earlier nephrology consultation may lead to better clinical outcomes due to earlier optimisation of care, such as closer hemodynamic status monitoring before renal function deteriorates further [119].

10.1.3 Alert systems

Interestingly, detecting AKI earlier does not necessarily lead to better clinical outcomes. A randomised control trial (RCT) tested a hospital electronic alert system where when one group of patients developed AKI, the covering provider and pharmacist were notified immediately by text [120]. Surprisingly, the intervention group did not show any improvement in change in creatinine, dialysis or 7-day mortality, and long-term follow-up at 30-days also did not reveal any benefits. Except in the surgical ward, the timing and percentage of patients receiving a nephrology consultation was also similar between the two groups. Even though the alert group in the surgical ward received renal consults and were put on dialysis more often, they also had a much higher mortality rate. The lack of improvement suggests that the early detection of AKI alone does not lead to more effective management.

10.2 Active prevention of perioperative hypotension

Perioperative haemodynamic control may play a key role in preventing postoperative AKI. Renal hypoperfusion is a key factor in the pathogenesis of AKI, and although significant blood loss is a surgical risk, intraoperative hypotension is not clearly defined. It has previously been documented using values of relative and absolute reduction in blood pressure [121, 122], and the absolute thresholds of 60–70 mmHg have been associated with an increased incidence of AKI morbidity [121, 123–125]. In major surgeries, goal-directed fluid resuscitation therapy (GDT) in conjunction with inotropic agents can be used to optimise cardiac output, maintaining intravascular volume and organ perfusion. Continuous haemodynamic monitoring would also allow for hypotension to be recognised and treated more quickly, and GDT has been found to decrease postoperative AKI risk [126]. The use of inotropes may decrease the need for fluids whilst a numeric blood pressure target may also prevent accidental fluid overload, which is associated with AKI risk. The severity and duration of intraoperative hypotension both contribute to AKI; a 2015 retrospective study of 5127 non-cardiac surgery patients showed that both longer duration of intraoperative hypotension at 11–20 min or > 20 min, and lower intraoperative MAP of < 55 or < 60 mmHg were associated with a graded nature of AKI risk [127], and this was supported by other studies [121]. However, possibly because of the heterogenous nature of GDT or high standards of care in the comparison groups, some studies investigating GDT found that it did not modify AKI risk [128, 129].

10.3 Current treatment guidelines

Current treatment is largely supportive. The 2012 KDIGO guidelines recommends administering isotonic crystalloids as first-line treatment and prevention of AKI, avoiding or considering alternatives to nephrotoxic agents such as aminoglycoside antibiotics and radiocontrast agents, tight glycaemic control to maintain normoglycemia, and close functional haemodynamic monitoring and management [7].

Blood pressure and cardiac output should be tightly controlled using fluids and vasoactive medication. Careful consideration is also required when determining what crystalloid to use. When isotonic saline was used in intravenous fluid expansion compared to chloride-poor solutions such as Plasma-Lyte® 148, it led to greater hyperchloraemia and decreased renal perfusion in healthy volunteers, and a greater incidence of renal impairment and higher serum creatinine levels in patients [130–132]. Currently, there is no single intravenous fluid that is universally advocated, and this is an area that may benefit from clearer guidance as neither the National Institute for Health and Care Excellence (NICE) clinical guideline 174 (intravenous fluid therapy in adults in hospital) nor NICE guideline 148 (Acute kidney injury: prevention, detection or management) suggest a preferred type of crystalloid to use in renal impairment [133, 134]. There is also a similar lack of consensus regarding which vasoactive medication is most effective at preventing AKI [7]. An algorithm for the management of AKI is shown in Fig. 2.

10.4 Treatments in development

Possible treatment options for existing AKI are constantly under investigation. A 2017 review determined that although many pharmacological treatments such as steroids, statins, sodium bicarbonate, recombinant atrial natriuretic peptide (ANP), ACE-I, N-acetylcysteine, furosemide, and fenoldopam have been investigated to prevent the development and deterioration of AKI, only dexmedetomidine has consistently produced promising results [16].

Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist that was approved by the United States Food and Drug Administration (FDA) for use in 1999. It is currently used in ICU as a sedative and

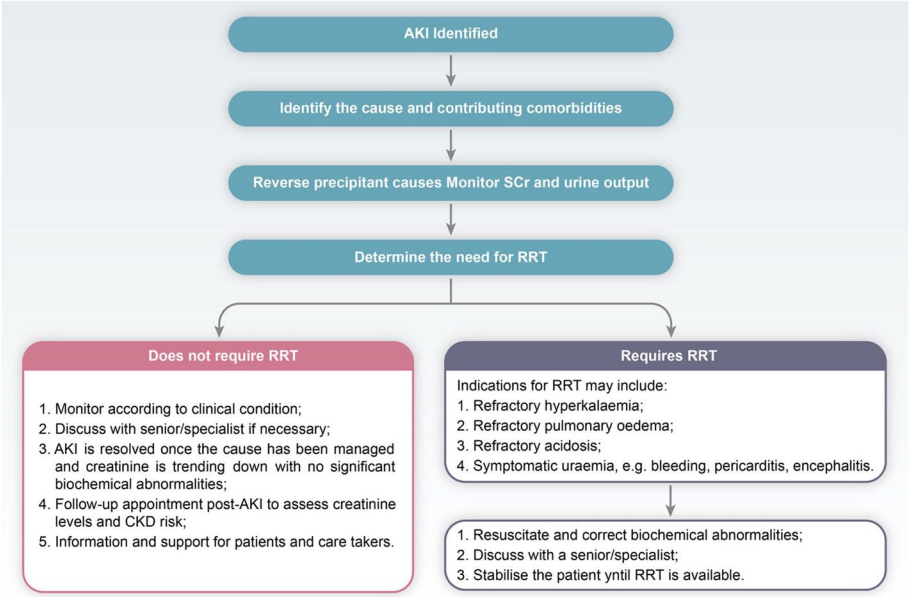


Fig. 2 An algorithm for the management of AKI based on the KDIGO guidelines and Boswell & Rossouw (CC BY 4.0). RRT: renal replacement therapy

analgesic-sparing agent and exhibits sympatholytic properties. It increases GFR, inhibits renin release [135], and increases sodium and water excretion [136]. In in-vitro and in vivo studies in mice, dexmedetomidine was found to minimise functional renal damage after ischaemia–reperfusion injury by suppressing toll-like receptor 4 (TLR-4) expression, one of the factors responsible for inflammation in AKI [137–139]. Further in vivo studies have also shown dexmedetomidine decreased the activation of Janus kinase 2 (JAK2), resulting in less phosphorylation of downstream inflammatory signal transducer and activator of transcription (STAT) factors STAT1 and STAT3, and greater renal recovery following renal ischaemia; dexmedetomidine also mediated a much lower pathological increase of intercellular adhesion molecule 1 (ICAM-1) during ischaemia–reperfusion injury, which likely contributes to its renoprotective effects [140]. In a RCT involving patients undergoing valvular heart surgery, those who received perioperative dexmedetomidine had a significantly lower AKI incidence and lower severity AKIN stage [141]. Similarly, a 2016 meta-analysis found that in paediatric cardiac surgery patients, prophylactic dexmedetomidine had positive effects on AKI incidence or all-cause mortality [142], and a 2021 retrospective cohort study of 2,068 cardiac surgery patients showed improved 5-year survival in those who received dexmedetomidine perioperative [143]. Given its renoprotective properties and ability to increase GFR, administering dexmedetomidine before renal ischaemic injury may benefit post-ischaemic renal recovery and attenuate tubular injury [24], and its administration before and after ischaemia–reperfusion injury may have protective effects on renal function [137]. Further studies are required to ascertain the exact method of administration in order to optimise its benefits [144, 145].

10.5 RRT timing in AKI prevention

It is unclear whether starting RRT earlier would help prevent AKI. Currently, most doctors choose to delay RRT as much as possible. The commencement of RRT is usually indicated by severe renal impairment, such as severe acidosis, hyperkalaemia, or fluid imbalance [7]. The benefits of initiating RRT before end-stage functional renal damage are being explored in research, and there is no guidance on the optimal timing. A 2018 Cochrane Review of ICU patients with AKI found that starting RRT early may reduce 30-day mortality and improve functional renal recovery [146] but can also lead to more patients experiencing adverse side effects such as catheter-related infections [146, 147]. However, a 2020 systematic review of recent RCTs found no difference in 28-day mortality between patients who received early RRT versus delayed RRT when the patients did not have urgent indications to start RRT [148].

11 Recommendations and directions for future research

Robust studies using different pharmacological agents such as dexmedetomidine should continue, especially amongst heterogenous populations. A greater focus

should be placed on modifiable preoperative risk factors and the management of comorbidities through better risk stratification. This would allow clinicians to take early definitive action to prevent worsening AKI severity [149]. All patients should have their baseline preoperative SCr measured so any perioperative renal impairment or pre-existing CKD can be identified and managed quickly. In emergency surgery or when cardiopulmonary bypass is required, renal function should be monitored closely. Postoperative scoring systems were much better predictors of post-surgical AKI development than preoperative scores, and this may suggest the greater importance of optimising postoperative factors [5, 24, 150].

12 Conclusion

Perioperative AKI is a common complication that leads to greatly increased risk of morbidity and mortality. Both short-term and long-term surgical outcomes are poor. Early renal impairment detection and preoperative risk stratification are vital to intervening early to preserve renal function and prevent AKI deterioration. The pathophysiology of renal dysfunction is complex and multifactorial, and pharmacological interventions need to be widely applicable to a heterogenous population. Further research of pharmacological treatments of AKI should be conducted in large-scale randomised controlled trials representative of the diverse population affected by AKI.

Abbreviations

ACE-I	Angiotensin-converting enzyme inhibitor
ADL	Activities of Daily Living
AKI	Acute kidney injury
AKI-D	AKI requiring dialysis
AKIN	Acute Kidney Injury Network
ANP	Atrial natriuretic peptide
APACHE	Acute Physiology and Chronic Health Evaluation
ASA-PS	American Society of Anesthesiologists Physical Status
ATP	Adenosine triphosphate
CABG	Coronary artery bypass graft
CKD	Chronic kidney disease
COX	Cyclooxygenase
CPB	Cardiopulmonary bypass
CRRT	Continuous renal replacement therapy
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GDT	Goal directed therapy
GFR	Glomerular filtration rate
HIC	High-income country
ICAM	Intercellular adhesion molecule
ICU	Intensive care unit
IL	Interleukin
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney injury molecule-1
L-FABP	Liver-type fatty-acid-binding protein
LMIC	Low or middle-income country
NAG	N-acetyl-β-D-glucosaminidase
NGAL	Neutrophil gelatinase-associated lipocalin
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
RCT	Randomised control trial
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
ROS	Reactive oxygen species
RRT	Renal replacement therapy
SAPS	Simplified Acute Physiology Score
SCr	Serum creatinine
SF-36	36-Item Short Form Survey
TLR	Toll-like receptor

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