BJA

British Journal of Anaesthesia, 115 (S2): ii3–ii14 (2015)

doi: 10.1093/bja/aev380
Clinical Practice

CLINICAL PRACTICE

Perioperative acute kidney injury

O. Goren* and I. Matot

Division of Anaesthesiology, Pain, and Intensive Care, Tel Aviv Medical Center, affiliated with Sackler Medical School, Tel Aviv University, Tel Aviv, Israel

*Corresponding author: E-mail: goren.orr@gmail.com

Abstract

Perioperative acute kidney injury (AKI) is not uncommon and is associated with considerable morbidity and mortality. Recently, several definition systems for AKI were proposed, incorporating both small changes of serum creatinine and urinary output reduction as diagnostic criteria. Novel biomarkers are under investigation as fast and accurate predictors of AKI. Several special considerations regarding the risk of AKI are of note in the surgical patient. Co-morbidities are important risk factors for AKI. The surgery in itself, especially emergency and major surgery in the critically ill, is associated with a high incidence of AKI. Certain types of surgeries, such as cardiac and transplantation surgeries, require special attention because they carry higher risk of AKI. Nephrotoxic drugs, contrast dye, and diuretics are commonly used in the perioperative period and are responsible for a significant amount of in-hospital AKI. Before surgery, the anaesthetist is required to identify patients at risk of AKI, optimize anaemia, and treat hypovolaemia. During surgery, normovolaemia is of utmost importance. Additionally, the surgical and anaesthesia team is advised to use measures to reduce blood loss and avoid unnecessary blood transfusion. Hypotension should be avoided because even short periods of mean arterial pressure <55–60 mm Hg carry a risk of postoperative AKI. Higher blood pressures are probably required for hypertensive patients. Urine output can be reduced significantly during surgery and is unrelated to perioperative renal function. Thus, fluids should not be given in excess for the sole purpose of avoiding or treating oliguria. Use of hydroxyethyl starch needs to be reconsidered. Recent evidence indicates a beneficial effect of administering low-chloride solutions.

Key words: acute kidney injury; perioperative complications; perioperative management; surgery

Editor's key points

- Perioperative acute kidney injury is associated with major morbidity and mortality.
- Use of serum creatinine in diagnosis is imperfect, and several novel biomarkers are under development to improve detection.
- Contributing factors include patient comorbidities, specific surgeries, nephrotoxins, fluid and blood management, and haemodynamic stability.

The term acute kidney injury (AKI) is used to describe a rapid deterioration (hours to days) of renal function. This rapid deterioration leads to accumulation of plasma waste products, such as urea and creatinine. Acute kidney injury is not an uncommon disorder and is associated with considerable morbidity and mortality. The definition of AKI has changed and evolved over the years, making the comparison of incidence and prevalence among studies difficult. It is estimated that 2–18% of all hospital inpatients acquire AKI.[1–3] The incidence of AKI is reported to be between 22 and 57% in critical care patients.[4 5] Unlike the traditional belief that patients recovering from AKI usually return to their baseline renal function, recent reviews of the literature show AKI to be a significant risk factor for chronic kidney disease.[6 7] Acute kidney injury is also known to induce distant organ damage, which in turn contributes further to morbidity and mortality.[8]

Accepted: October 3, 2015

Perioperative AKI is a leading cause of morbidity and mortality. It is associated with increased risk of sepsis, anaemia, coagulopathy, and mechanical ventilation.[9] In a prospective study of 1200 patients having non-cardiac non-vascular surgery, AKI was associated with increased morbidity and mortality.[10] A study investigating patients after general surgery reported an eight-fold increase in mortality in patients with perioperative AKI,[11] whereas a more recent large-scale study of patients undergoing intra-abdominal surgery found that non-AKI patients had a 30 day mortality of 1.9%, compared with 31% in patients with AKI.[12] Notably, mortality is higher in patients with perioperative AKI even after complete renal recovery.[9]

Perioperative AKI is a feared phenomenon with deleterious effects. Methods to ameliorate the burden of perioperative AKI are constantly sought. In this review, we discuss definitions of AKI, the pathophysiology of AKI relevant to the perioperative period, and specific considerations of AKI that are of special relevance in the surgical patient. With this knowledge, we consider methods to identify patients at risk of AKI and review the current recommended perioperative management aimed to prevent perioperative AKI.

Definition of acute kidney injury

The first attempts to define AKI date back to the 17th century. Nevertheless, the term acute renal failure appeared for the first time in 1951.[13] Since then, many definitions have been used by investigators and clinicians, resulting in a lack of clarity and preventing comparable research. A review on the different classification systems found more than 35 definitions of acute renal failure.[14] The various definitions attempted to describe diverse aspects of AKI. Glomerular filtration rate (GFR) roughly expresses the overall function of the different parts of the kidney; a rapid decline in GFR defines AKI.[15] Given that a 24 h urine creatinine clearance test is not straightforward to apply in everyday practice, serum creatinine (sCr) change from baseline is considered a reasonable substitute and is roughly correlated with the change in GFR (although sCr becomes abnormal only after GFR declines significantly).[2] Most definitions use urine output and sCr as markers of renal function because they are unique to the kidney and easily measured.

The first publication of consensus criteria for AKI was published in 2004. The system was named RIFLE (risk, injury, failure, loss of kidney function, end-stage renal failure) and used sCr or urine output to define AKI.[16]

In 2004, the term AKI was proposed as a replacement for the former acute renal failure. The change of terms highlighted the fact that loss of function and failure are preceded by a structural and physiological injury to the kidney. Later, in 2007, a modified definition of the RIFLE criteria was published by the Acute Kidney Injury Network (AKIN).[17] Although the AKIN criteria evolved from the RIFLE criteria, a major advance was the understanding that even small changes in sCr concentrations are associated with increased morbidity and mortality.[18 19] The AKIN criteria allowed definition of AKI even without knowledge of baseline sCr.

Several studies conducted on postoperative AKI attempted to compare the predictive value of the two methods.[20 21] Both schemes predict outcome of AKI with different sensitivity and specificity. The comparison also highlighted the need to select baseline sCr carefully when the diagnosis of AKI is based solely on the net sCr change. If the selected baseline sCr is the first postoperative sCr or the sCr after fluid resuscitation, over-diagnosis of AKI can occur.[21]

In 2012, a clinical practice guideline of AKI was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) Foundation. The guideline includes a comprehensive review of AKI definition, risk assessment, diagnosis, prevention, treatment, and renal replacement therapy. The group accepted the existing RIFLE and AKIN criteria for the definition of AKI and proposed simple, practical criteria of AKI.[22] The KDIGO criteria include both a relative and an absolute change of sCr and accept a short (48 h) and an extended (7 days) time frame for diagnosis of AKI. The urine output criteria remained practically unchanged. The KDIGO recommendations relevant to perioperative AKI are discussed in the perioperative management section.

A comparison of the three different classifications is presented in Table 1.

Despite the continued effort to standardize the definition of AKI using sCr, these methods have several flaws. The increase in sCr is late in the course of AKI such that by the time the diagnosis is made using standard laboratory methods the disease is well established. In addition, sCr can be influenced by volume overload, nutrition, steroids, and muscle trauma.[2]

Recently, major advances suggest that biomarkers might help to detect AKI early, identify the aetiology, predict outcome, and tailor specific therapies. Biomarkers are molecules that report on renal function or damage that relate specifically to different biological functions of the kidney.[23] For example, *N*-acetyl-β-d-glucosamininidase in the urine is a direct marker of lysosomal injury in the proximal tubule, whereas cystatin C in the urine is a marker of reduced uptake by damaged proximal tubules.[23] Some other promising biomarkers are kidney injury molecule-1, microalbumin, neutrophyl gelatinase-associated lipocalin, interleukin 18, and liver fatty acid binding protein.[23 24] A promising study conducted in intensive care units (ICUs) showed that the combined use of the two novel biomarkers insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases-2 was a sensitive and fast way to detect AKI.[25] A similar study showed that insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases-2 can also be used for the detection of post-cardiac surgery AKI.[26]

Several issues remain to be solved before these biomarkers can be used in clinical practice. For example, should urinary biomarkers be normalized to urinary creatinine concentrations?[27] What is their specificity and sensitivity? Can we accurately define the sensitivity and specificity when making comparisons with a rather imperfect gold standard, such as sCr? Should a single biomarker or a combination of several be used?[24]

A major issue concerning AKI criteria is their relevance to the perioperative period. Many surgical patients arrive in hospital without preoperative sCr concentrations. As was mentioned above, this can lead to over-diagnosis of AKI. On the contrary, when patients do arrive with a preoperative sCr concentration, the opposite can occur because in the immediate postoperative period sCr concentrations can be lower than baseline as a result of haemodilution after massive fluid administration and fluid shifts. Comparing these postoperative and preoperative values can lead to under-diagnosis of AKI and consequently delay treatment.

A major concern is whether or not intraoperative urine output is reliable as a criterion for AKI. As discussed below, recent studies suggest that urine output can be reduced significantly during surgery and is unrelated to perioperative renal function.[28 29]

Mechanisms of perioperative acute kidney injury

Causes of AKI were traditionally divided into prerenal, intrinsic, and postrenal, which provides a convenient classification, but

Table 1 Comparison of the three classifications and staging of acute kidney injury: RIFLE, AKIN, and KDIGO criteria.[16 17 22] AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, risk, injury, failure, loss of kidney function, end-stage renal failure; RRT, renal replacement therapy; sCr, serum creatinine

Definition system	RIFLE 7 days	AKIN 48 h	KDIGO
Staging	**Risk** Increased sCr × 1.5 or GFR decrease >25% or urine output <0.5 ml kg^{-1} h^{-1} for 6 h	**Stage 1** Increased sCr × 1.5–2 or sCr increase ≥0.3 mg dl^{-1} or urine output <0.5 ml kg^{-1} h^{-1} for >6 h	**Stage 1** Increased sCr × 1.5–1.9 that is known or presumed to have occurred within the preceding 7 days or sCr increase ≥0.3 mg dl^{-1} within 48 h or urine output <0.5 ml kg^{-1} h^{-1} for 6–12 h
	Injury Increased sCr × 2 or GFR decease >50% or urine output <0.5 ml kg^{-1} h^{-1} for 12 h	**Stage 2** Increased sCr × 2–3 or urine output <0.5 ml kg^{-1} h^{-1} for >12 h	**Stage 2** Increased sCr × 2–2.9 or urine output <0.5 ml kg^{-1} h^{-1} for ≥12 h
	Failure Increased sCr × 3 or GFR decrease 75% or sCr ≥4 mg dl^{-1} when sCr is in acute increase (≥0.5 mg dl^{-1}) or urine output <0.3 ml kg^{-1} h^{-1} for 24 h or anuria for 12 h	**Stage 3** Increased sCr × 3 or more or sCr ≥4 mg dl^{-1} when sCr is in acute increase (≥0.5 mg dl^{-1}) or urine output <0.3 ml kg^{-1} h^{-1} for >24 h or anuria for 12 h	**Stage 3** Increased sCr × 3 or sCr ≥4 mg dl^{-1} or initiation of RRT or GFR decrease to <35 ml min^{-1} (1.73 m)$^{-2}$ in patients <18 yr old or urine output <0.3 ml kg^{-1} h^{-1} for ≥24 h or anuria for ≥12 h

the disease does not always strictly obey these definitions. For example, prerenal AKI if profound and lasting will eventually lead to intrinsic AKI (secondary AKI).[2 15] Intrinsic AKI is better understood when divided into the major structures of the kidney, as follows: (i) damage to the renal vasculature from embolic events and vasculitides, such as malignant hypertension and haemolytic uraemic syndrome; (ii) damage to the renal interstitium from allergic reactions, leukaemia, lymphoma, and bacterial infections; (iii) tubular damage because of secondary AKI, inflammation, exogenous toxins (contrast dye, antibiotics), and endogenous toxins (myoglobin, haemoglobin).[15] The most common trigger for AKI in the inpatient population is sepsis.[2 30] Major surgery and acute decompensated heart failure are also common reasons for AKI in this population.[2]

The kidney is able to maintain GFR even in the face of changing arterial pressure and volume status. Reduced mean arterial pressure (MAP) initiates a series of systemic and local processes. The sympathetic system is activated, antidiuretic hormone is released, and the renin–angiotensin–aldosterone system increases angiotensin II activity. The net result is water retention, increased sodium absorption, and the preservation of GFR.[15 31] Later, if hypoperfusion is not corrected, angiotensin II eventually causes vasoconstriction of both the afferent and the efferent arterioles, and as a consequence, reduces GFR.[31] These mechanisms function only as long as MAP is maintained above the autoregulatory threshold. Below a MAP of 75–80 mm Hg, the autoregulatory efficiency declines abruptly.[15]

A wider and more complex understanding of the mechanisms of AKI is emerging. The simple ischaemia model alone cannot explain sepsis- and major-surgery-associated AKI. Haemodynamics in sepsis are dominated by a hyperdynamic state, and global renal blood flow may remain intact.[30] Decreased perfusion might not be the only reason for major-surgery-associated AKI, because even prolonged intervals of partial occlusion of the renal artery are well tolerated.[2] Evidence suggests that systemic inflammation leading to tubular injury is responsible for sepsis-associated AKI whether or not ischaemia was the initiating factor.[30]

Apart from the general mechanisms that are common to AKI from various causes, other specific contributions to perioperative AKI are of special note in the surgical patient.

Co-morbidities

With the development of surgical techniques and advanced anaesthesia delivery and monitoring, surgery on sicker and older patients is more common. These patients suffer from co-morbidities, such as chronic kidney disease, metabolic syndrome, diabetes mellitus, and cardiovascular and hepatobilliary disease, all of which are well-documented risk factors predisposing to AKI.[10–12 32] Male sex is also a risk factor of AKI.[11] Other reported risk factors in surgical patients are functional dependence, ventilator dependence, chronic obstructive pulmonary disease, smoking, bleeding disorders, chronic steroid use, and cancer.[12] A retrospective cohort study evaluated the incidence of AKI in patients admitted to the ICU beds of the postanaesthesia care unit. Independent risk factors of AKI included ASA physical status, Revised Cardiac Risk Index, high-risk surgery, and congestive heart failure.[33] A prospective cohort study conducted in non-vascular, non-cardiac surgery patients identified age, diabetes mellitus, Revised Cardiac Risk Index, and ASA status as independent risk factors of AKI.[10]

Obesity

Obesity is an excessive accumulation of adipose tissue. Obesity is an epidemic with profound effect on morbidity and mortality. Worldwide, the prevalence of BMI >25 kg m^{-2} is estimated to be 37% in men and 38% in women.[34] Obesity is a risk factor for AKI

in general and for perioperative AKI in particular;[35 36] it is associated with metabolic syndrome and can alter renal hemodynamics.[37] The special characteristics of the kidney in the obese, known as obesity-related glomerulopathy, include changes in GFR and glomerulomegaly.[35] A different understanding of the correlation between obesity and atherosclerotic morbidity can be achieved when the different types and spread of adipose tissue are taken into consideration.[38 39] Recently, a study on ICU trauma patients showed AKI to be correlated with abdominal fat in particular, as measured by computed tomography.[40]

Surgery

In every major operation, a risk for reduction in effective blood volume or mechanical obstruction exists. Hypovolaemia, low systemic vascular resistance because of anaesthesia or caval compression, and direct injury to the renal system are all common events during surgery that can harm the kidney.

Emergency surgery is a risk factor for AKI.[11 12] Patients with sepsis presenting to the operating room are at increased risk of AKI,[12] as are patients arriving in the emergency room with sepsis.[41] Major vascular surgery,[42] and cardiac surgery in particular,[43] are well-known risk factors for AKI. Patients undergoing intraperitoneal surgery in general,[11] and exploratory laparotomy and small bowl resections in particular, are more prone to develop AKI.[12] Lung resection has a relatively high incidence of AKI.[44] An observational study on cardiac surgery because of infective endocarditis showed the incidence of postoperative AKI to be as high as 59%.[45]

Intra-abdominal pressure

Increased intra-abdominal pressure is common in ICU patients after abdominal surgery.[46] Increased intra-abdominal pressure, which is frequently explained by excessive administration of fluids,[47 48] can cause abdominal compartment syndrome, mechanically compress the renal veins and constrict the renal arteries via activation of the sympathetic system.[48] Increased intra-abdominal pressure can ultimately lead to reduced renal perfusion and create an ischaemic insult to the kidney and AKI.[48 49] Laparoscopy can also lead to a transient increase in intra-abdominal pressure. As a result, during laparoscopy the recorded urine output is significantly reduced, and patients can become oliguric despite normovolaemia and normotension. Several studies have shown that the observed reduction in urine output during laparoscopy is not predictive of postoperative AKI in adults[50–52] and in children.[53] In the critically ill and in patients' suffering from chronic kidney disease, the duration of pneumoperitoneum should be minimized.[54]

Anaesthesia

The anaesthetist can influence the risk of AKI in several ways. Haemodynamic management (in particular, keeping MAP >55 mm Hg)[55 56] and maintenance of euvolaemia are both related to the occurrence of perioperative AKI. Historically, some halogenated anaesthetics are considered nephrotoxic, such as methoxyflurane, which is no longer in routine use.[57] Use of sevoflurane is associated with increased plasma fluoride concentrations and with production of a haloalkene called 'compound A'; however it has been evaluated extensively and is considered safe to use.[58] Regarding the choice of anaesthetic technique, most reports concern the beneficial effects of inhaled anaesthetics and propofol to attenuate AKI in experimental studies; however, such an effect has not been shown in humans.[59–62] Recently, a study conducted on 112 patients undergoing valvular heart surgery and randomized to anaesthesia by either propofol or sevoflurane showed anaesthesia with propofol to be associated with reduced incidence and severity of AKI.[63] A study on healthy volunteers found that the sympathetic block caused by epidural anaesthesia did not change renal blood flow significantly.[64] A meta-analysis found the incidence of AKI to be lower for neuraxial anaesthesia when compared with general anaesthesia.[65] Another meta-analysis evaluated epidural anaesthesia combined with general anaesthesia in cardiac surgery and found a reduction in AKI in the combined group.[66] A recent population-based historical cohort study found combined general and neuraxial anaesthesia to have a similar incidence of AKI when compared with general anaesthesia alone.[67]

Cardiac surgery

Acute kidney injury is a significant deleterious consequence of cardiac surgery that is associated with increased mortality.[19 68] The incidence of AKI associated with cardiac surgery can reach 30% depending on the definition of AKI.[68–70] The mechanisms of cardiac surgery-associated AKI are multifactorial and mostly related to the use of cardiopulmonary bypass (CPB). Some of the pathophysiological explanations are ischaemia–reperfusion injury, microembolization, inflammation, decreased renal perfusion pressure, haemodilution, and use of nephrotoxic drugs.[43] Preoperative chronic kidney disease is the most important risk factor for perioperative AKI in this setting. Other risk factors of cardiac surgery-associated AKI are age, female gender, preoperative anaemia, perioperative packed red blood cell (PRBC) transfusion, heart failure, emergency surgery, diabetes mellitus, haemodilution on CPB, duration of CPB, use of an intra-aortic balloon pump, and valve surgery.[43 71] Several risk-predicting models of cardiac surgery-associated AKI have been proposed in order to increase vigilance for high-risk patients.[72–74]

Methods to prevent cardiac surgery-associated AKI have been reported with varying degrees of evidence. Preoperative methods include the use of aspirin, avoiding diuretics, maintaining euvolaemia, avoiding anaemia, use of erythropoietin, and use of prophylactic renal replacement therapy. Intraoperative methods are avoiding anaemia and PRBC transfusion, maintaining MAP above cerebral perfusion pressure, pulsatile perfusion during CPB, preferring off-pump coronary artery bypass grafting, use of intra-aortic filtration, and use of miniature CPB. The main postoperative strategy to prevent the consequences of cardiac surgery-associated AKI is early use of renal replacement therapy.[43] Some pharmacological protective agents have been proposed (fenoldepam, statins, human atrial natriuretic peptide, and nesiritide) but without conclusive evidence to support their use.[43] Recently, remote ischaemic preconditioning was shown to reduce the incidence of cardiac surgery-associated AKI and the need for renal replacement therapy in high-risk patients.[75]

Paediatric surgery

Data on paediatric perioperative AKI is scarce. Although the neonatal period is relatively short, the AKI burden is disproportionally high in this age group.[76 77] Acute kidney injury in children is associated with long-term morbidity and mortality.[77–79] The most common cause in neonates and infants is post-cardiac surgery AKI.[77] Paediatric AKI is defined in a similar way to adult AKI, with some modifications,[80] with the exception of the first days of

life when the neonate's sCr reflects the mother's sCr.[81 82] Later, neonatal GFR (evaluated as sCr) is correlated with gestational age and postnatal age in preterm neonates.[82] High vigilance for AKI is necessary in the paediatric population, especially in children admitted to the paediatric ICU. Several methods have been proposed for the early detection of AKI, but with various degrees of success.[83–85] Cardiac surgery-associated AKI in children has many risk factors, but the two consistent ones are prolonged CPB and younger age.[85] Currently, the early management of paediatric AKI involves identification of patients at risk, optimizing volume status, and administering theophylline for neonates suffering from severe asphyxia.[22 31]

Transplantation surgery

Transplantation surgery is usually a complex procedure in high-risk patients. Acute kidney injury complicates many of these procedures. Transplanted kidneys are susceptible to surgical, ischaemic, and drug-related insults predisposing them to AKI. However, application of the regular definitions of AKI to a transplanted kidney is more problematic considering the post-operative changes in sCr concentrations. Moreover, it is not always possible to differentiate accurately between perioperative AKI and graft dysfunction.[86]

Liver transplantation is a major high-risk surgery. The effects of cirrhosis, nephrotoxicity of some immunosuppressive drugs, and the risks of the surgery are all well-known risk factors for perioperative AKI. The incidence of post-liver transplantation-related AKI varies from 14 to 78% depending on the definition of AKI used, type of transplantation, and patients included in the study.[87–89] However, liver transplantation-related AKI has specific diagnostic problems attributable to high bilirubin concentrations, muscle wasting, oedema, and postoperative use of GFR-lowering medications, such as tacrolimus. All can affect sCr concentrations and under- or overestimate the incidence of AKI.[90] While some risk factors for liver transplantation-related AKI are similar to other high-risk surgeries, some risk factors are unique.[87 89 91] Accordingly, strategies to prevent liver transplantation-related AKI include the use of terlipressin[87] and avoiding or lowering the dose of tacrolimus after surgery.[92]

A small-scale study found the incidence of AKI post-lung transplantation to be 54%. The incidence of AKI among patients who had a double lung transplant was almost double (87%) the incidence in one-lung transplant patients (40%). Intraoperative hypoxaemia was correlated with AKI.[93]

Drugs

Nephrotoxic drugs are a well-established cause of AKI of prerenal, postrenal, and intrinsic origin. Nephrotoxic drugs are involved to some extent in AKI in up to 25% of critically ill patients.[2 94] A large population-based study showed that combinations of more than two prevalent nephrotoxic drugs (diuretics with angiotensin receptor blocker or angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs) increased the risk of AKI.[95] Angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs, in particular, may worsen prerenal AKI because of their influence on compensatory mechanisms aimed to maintain GFR.[15] Aminoglycoside, a commonly administered antibiotic in the operating room, can cause AKI through intracellular processes such as mitochondrial dysfunction and reduction of protein synthesis. A high dose of aminoglycoside, chronic kidney disease, hypovolaemia, diabetes mellitus, and old age are all risk factors for aminoglycoside-induced nephrotoxicity.[15]

Iodinated radiocontrast-induced acute kidney injury

Contrast dye-induced AKI is a subtype of drug-induced AKI with well-defined characteristics. The pathophysiology of contrast dye-induced AKI is a combination of hypoxic and toxic damage and endothelial dysfunction.[15] It is not uncommon for patients to arrive in the operating room after a radiological examination involving radiocontrast dye. Contrast dye-induced AKI is associated with a significant increase in both short- and long-term mortality.[96] Contrast dye-induced AKI can be prevented by maintaining normovolaemia, augmenting urine output, and withholding other nephrotoxic agents. Other strategies include the administration of sodium bicarbonate and *N*-acetyl cysteine, although evidence is not well established for these treatments.[22 97] Patients with hypovolaemia are at increased risk of contrast dye-induced AKI. Maintaining effective blood volume is essential before exposing patients to the risks of drugs and contrast dye.[15 22]

A summary of possible insults predisposing to AKI in the perioperative period is presented in Fig. 1.

Perioperative management

Identification of patients at risk of developing acute kidney injury

The first step in preventing and treating AKI is to identify patients at risk. Extremes of age, co-morbidities, anaemia, potential hypovolaemia, use of contrast dye, use of nephrotoxic drugs, and emergency or high-risk surgery should all alert the anaesthetist to the possibility of perioperative AKI. Some of these risk factors can be optimized before surgery.

Haemodynamic goals

The main haemodynamic goal in the perioperative patient is to prevent tissue hypoperfusion and thus organ hypoxia. Direct monitoring of tissue hypoxia is not readily feasible in the clinical setting. Thus, indirect measures, such as MAP, heart rate variability, and lactate concentrations, are usually used. In the ICU setting, MAP >60–65 mm Hg (>75 mm Hg in patients with chronic hypertension) is recommended to prevent AKI.[98 99] The perioperative patient has been less extensively investigated. A meta-analysis showed perioperative haemodynamic optimization to reduce postoperative AKI.[100] A study conducted on 33 300 non-cardiac surgery patients found that duration of MAP <55 mm Hg was independently correlated with AKI.[55] A recent retrospective cohort study conducted on 5127 patients undergoing non-cardiac surgery found similar results. The risk of AKI was increased when MAP was <60 mm Hg for >20 min or <55 mm Hg for >10 min.[56] These large-scale studies aid the anaesthetist in determining an MAP threshold to be maintained during surgery. They also emphasize the importance of the duration of hypotension, because even short periods have been shown to affect the kidney. Given that autoregulation changes with co-morbidities, future studies should take into account baseline MAP and possibly adopt a more personalized approach to intraoperative arterial pressure management.

Choice of fluid solution

Perioperative fluid therapy is aimed to maintain intravascular volume and allow tissue perfusion. Crystalloid solutions include

Aetiologies of perioperative acute kidney injury

Prerenal:

Preoperative	Intraoperative
1. Hypovolaemia	1. Hypovolaemia
Gastrointestinal loses	Insensible loses
Haemorrhage	Haemorrhage
Third spacing	Over diuresis
2. Sepsis	2. Hypotension due to low systemic vascular resistance (anaesthesia induced)
3. Cardiac failure	3. Low cardiac output (heart failure, anaesthesia and CPB induced)
4. Increased intra-abdominal pressure	4. Increased intra-abdominal pressure
5. Cirrhosis, hepatorenal syndrome	5. Aortic cross-clamp
Drugs-non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, norepinephrine, diuretics.	

Intrinsic:

Perioperative
Inflammation
Patient co-morbidities-chronic kidney disease, diabetes mellitus, obesity, atherosclerosis.
Drug-induced-Antibiotics, aspirin, phenytoin, furosemide, non-steroidal anti inflammatory drugs, clopidogrel, tacrolimus
Radio-contrast agents
Endogenous nephrotoxins-haemoglobin and myoglobin
Acidosis
Infection
CPB
Anaemia
Packed red blood cell administration
Fluid solutions (hydroxyethyl starch, chloride-rich solutions)

Postrenal:

Preoperative	Intraoperative
Tumour	Surgical intervention or damage
Prostatic enlargement	
Calculi	
Blood clots	
Neurogenic bladder	

CPB-Cardio-pulmonary bypass.

Fig 1 Aetiologies of perioperative acute kidney injury.

normal saline (0.9%) or balanced solutions (Ringer's lactate, Plasma-Lyte, etc.). Colloid solutions include synthetic hydroxyethyl starches (HES), gelatins, and albumin.

Crystalloid solutions contain different mixtures of electrolytes. Saline contains only NaCl, unlike balanced crystalloids, which are more similar to plasma content. Use of 0.9% saline is associated with development of hyperchloraemia. Animal[101] and human experiments[102] suggest that saline infusion is correlated with reduced renal blood flow compared with balanced solutions. In a large study in the ICU, chloride-restricted fluid management was associated with less AKI and renal replacement therapy.[103] Similar results were observed in liver transplantation patients, where chloride-liberal fluid administration was a risk factor for postoperative AKI.[104] Another large retrospective study found postoperative hyperchloraemia to be correlated with postoperative AKI.[105] The precise clinical implications of these results for the incidence of perioperative AKI are not yet clear and are under investigation.[106 107]

The association of colloid solutions with AKI is controversial. Several recent studies report an increase in incidence of AKI and renal replacement therapy in critically ill patients infused with HES rather than crystalloids.[108–111] These studies evaluated HES solutions with different molecular weights, including the new low-molecular-weight solutions. Less is known about surgical patients during the perioperative period. Several studies and meta-analyses found HES to be a risk factor for AKI,[91 112 113] whereas others did not.[114–117] To date, intraoperative use of HES solutions is not recommended in patients with AKI or at risk of

Preoperative:

Identify patients at risk:

Patient related factors- co-morbidities (obesity, CKD, DM, cardiovascular and hepatobilliary diseases, male sex, obesity, pulmonary disease, steroid use, cancer, ASA score, ICU patients, increased intraabdominal pressure, sepsis, older age and neonates)

Procedure related factors- a. Major surgery (extensive laparotomy lung resections, transplantations)
b. Emergency surgery
c. Cardiac surgery
d. Use of contrast dye

Anaemia- Correct anaemia before to surgery when possible according to the patient blood management protocol.† [139 140 141 142 143 145]

Intraoperative:

Choice of fluid solution- a. Avoid HES solutions when possible.† [22 91 108 112 113 117 118 119]
b. Balanced crystalloid solutions may prove superior to chloride rich solutions in preventing AKI.† [103 104 105]

Fluid management- a. The use of intraoperative urinary output as a guide to fluid administration may not be beneficial.† [127 128 129 130]
b. Avoid the use of diuretics unless a need to treat volume overload arises.[22 98 135 136 137]
c. Use measures during surgery to avoid blood loss and unnecessary PRBC transfusion.† [139 140 141 142 143 145]

Haemodynamic goals- a. Avoid a low MAP even for relatively short periods of time.† [55 56]
b. Evidence so far do not recommend the use of one vasopressor over the other.[22]
c. Low dose dopamine is no longer considered "renoprotective" and is not recommended.[22 98 148]

General considerations- a. Avoid the use of aminoglycosides unless no suitable less nephrotoxic alternative exists.[22]

Fig 2 Perioperative management, recommendations prevention of acute kidney injury, and summary. CKD, chronic kidney disease; DM, diabetes mellitus; HES, hydroxyethyl starch; ICU, intensive care unit; MAP, mean arterial blood pressure; PRBC, packed red blood cell. †This recommendation is based mainly on observational studies, randomized controlled trials are needed.

AKI.[91 108 112 117 118] In a recent paper, Hartog and colleagues[119] raised concerns regarding the intraoperative use of HES and concluded that in the absence of proven benefit and considering the methodological problems with studies supporting the use of HES, they do not recommend use of HES solutions in any clinical situation.

Intraoperative fluid management and urine output

A common practice to maintain effective blood volume and thus kidney perfusion is i.v. hydration. Correcting hypovolaemia is an essential perioperative haemodynamic goal,[120] and appropriate hydration is considered important for the avoidance of AKI.[22 121] Intraoperative urine output is often monitored but rarely responds to fluid administration.[122–126] Clearance of fluid during general anaesthesia is only a small fraction of that observed in conscious volunteers.[127] Infusion of crystalloids during anaesthesia shows reduced clearance and slower distribution[28 29] such that intraoperative oliguria may not reflect fluid status or predict future AKI. A retrospective study in non-cardiac surgical patients that evaluated risk factors associated with AKI did not find oliguria to be predictive of postoperative AKI.[128] Two prospective randomized studies[129 130] that involved bariatric patients and patients undergoing thoracoscopic surgery for lung resection found no correlation between intraoperative urine output and postoperative AKI. In both studies, intraoperative oliguria was not predictive of postoperative AKI. Additionally, both studies found no relationship between the amount of

intraoperative fluids administered (very restrictive *vs* high-volume fluid administration) and intraoperative urine output or postoperative renal dysfunction. Given that liberal fluid administration can be correlated with worse postoperative outcome,[123–125 131 132] the recommendation to maintain, among other things, urine output of at least 0.5 ml kg^{-1} h^{-1} should be reconsidered.[133 134] Urine output in anaesthetized patients may not be an adequate indicator of fluid balance and is not predictive of postoperative AKI in elective surgeries (non-vascular, non-cardiac, and non-transplant).

Use of diuretics

Loop diuretics and mannitol are commonly used during surgery in an attempt to prevent AKI or treat oliguria and anuria based on experimental studies reporting renoprotective properties of diuretics. This practice has not been shown to be benefiial.[135] On the contrary, use of diuretics can be harmful because these agents can cause prerenal damage and nephrotoxicity. Diuretics are not recommended except to treat volume overload.[22 98 135–137]

Anaemia and use of blood products

Low haemoglobin concentration reduces the oxygen-carrying capacity of the blood. Experimentally, medullary hypoxia plays a central role in the development of AKI.[138] A large observational study involving non-cardiac surgery patients found preoperative anaemia and early postoperative decrements of haemoglobin to be associated with AKI.[139] Perioperative anaemia and perioperative PRBC transfusions are risk factors for AKI in cardiac surgery,[140–143] such that every unit of transfused blood increases the incidence of cardiac surgery-associated AKI by 10–20%.[141] The extent to which this increase is attributable to the deleterious effects of PRBC transfusions or is a surrogate marker for an extensive surgery is not known. A synergism between the effects of anaemia and PRBC transfusion may also play a role in this complex mechanism of injury.[140 141] Additionally, stored PRBCs can cause organ damage and are associated with reduced oxygen-carrying capacity.[141 144] It is therefore advisable to optimize patients' preoperative haemoglobin status as suggested by the recent 'patient blood management' protocol,[145] while using measures during surgery to reduce blood loss and avoid unnecessary PRBC transfusion.

Use of vasopressors

The role of vasopressors in preventing AKI is not entirely clear. The benefit of vasopressor use in the setting of AKI is maintenance of renal perfusion pressure within autoregulatory limits. Nevertheless, concerns about renal vascular vasoconstriction and side-effects cause clinicians to refrain from their use. Norepinephrine constricts renal arterioles and reduces renal blood flow (but not GFR).[146] Nonetheless, it is commonly used and is considered safe and effective.[98 147] Vasopressin in addition to norepinephrine did not show clinical benefit.[147] Epinephrine has a prominent α-adrenoreceptor-mediated effect in the kidney. Epinephrine is more rarely used, mainly because of its potential to cause tachycardia, lactataemia, and hyperglycaemia.[147] Low-dose dopamine can enhance urine output through its diuretic effect but is no longer considered renoprotective and is not recommended for treatment of AKI.[22 98 148] Compared with norepinephrine, dopamine is associated with more adverse events.[149] Phenylephrine is a potent vasoconstrictor, but with a profound α-adrenergic activity that causes vasoconstriction. The current KDIGO guidelines state that the evidence so far does not support the use of one vasoactive agent over another.[22]

Vasodilator therapy

The rationale behind vasodilator therapy (fenoldepam, atrial natriuretic peptide, nesiritide) is to cause renal vasodilatation and increase GFR. Taking into consideration the lack of conclusive beneficial evidence and the potential adverse effects of vasodilator therapy, the common recommendation is against their use to prevent or treat AKI.[22 150]

A summary of the major recommendations for prevention of AKI is presented in Fig. 2.

Conclusions

Perioperative AKI continues to be a feared consequence of surgery. It is associated with both short- and long-term deleterious effects. The complexity of perioperative AKI pathophysiology involves the combined roles of ischaemia and inflammation as causes of AKI. Novel biomarkers are proposed as a faster and more accurate way for prompt identification of AKI and could prove beneficial in early intervention to prevent further deterioration in renal function. Specific co-morbidities, surgeries, and interventions increase the risk of AKI, such as cardiac or transplant surgery and use of contrast dye. The intraoperative period is unique in that both anaesthesia and surgery combine to affect renal function. During surgery, even short periods of hypotension put the kidney at risk. Urine output does not predict postoperative AKI. Careful selection and use of i.v. fluids and vasopressors and appropriate blood management are important to prevent perioperative AKI.

Authors' contributions

Drafted the manuscript: O.G.
Reviewed and revised the manuscript: I.M.
Approved the final manuscript: O.G., I.M.

Declaration of interest

None declared.

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Handling editor: H. C. Hemmings