Perioperative renal protection

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Purpose of review
The present article reviews the recent literature on the main aspects of perioperative acute kidney injury (AKI).

Recent findings
AKI occurs in 1 in every 10 surgical patients, with cardiac, orthopedic, and major abdominal surgeries being the procedures associated with the highest risk. Overall, complex operations, bleeding, and hemodynamic instability are the most consistent procedure-related risk factors for AKI. AKI increases hospital stay, mortality, and chronic kidney disease, gradually with severity. Furthermore, delayed renal recovery negatively impacts on patients' outcomes. Cell cycle arrest biomarkers seem promising to identify high-risk patients who may benefit from the bundles recommended by the Kidney Disease: Improving Global Outcomes guidelines. Hemodynamic management using protocol-based administration of fluids and vasopressors helps reducing AKI. Recent studies have highlighted the benefit of personalizing the blood pressure target according to the patient's resting reference, and avoiding both hypovolemia and fluid overload. Preliminary research has reported encouraging renoprotective effects of angiotensin II and nitric oxide, which need to be confirmed. Moreover, urinary oxygenation monitoring appears feasible and a fair predictor of postoperative AKI.

Summary
AKI remains a frequent and severe postoperative complication. A personalized multicomponent approach might help reducing the risk of AKI and improving patients' outcomes.

Keywords
acute kidney injury, fluids, renal replacement therapy, surgery

INTRODUCTION

The global volume of surgery is large and continues to grow over time. Between 2004 and 2012, the number of operations performed worldwide increased from 234.2 to 312.9 million, which represents a 33.6% augmentation over 8 years [1]. Thus, surgical care is a major component of the healthcare system, associated with increased life expectancy, although significant differences exist according to the economic environment [1]. Therefore, improvements in perioperative care is fundamental and should be considered a healthcare priority.

Postoperative complications are not uncommon and are associated with significant morbidity and mortality [2]. Moreover, such complications increase treatment costs [3] and decrease quality of life [4,5]. A recent international prospective study reported that 1 in every 6 patients experiences at least one complication after an operation, and 1 in every 35 who experiences a complication ultimately die during the hospitalization [2]. In this study, acute kidney injury (AKI) was the fourth most common complication after postoperative bleeding, surgical site infection, and arrhythmia.

The purpose of the present article is to review the recent literature on the main aspects of AKI diagnosis and management in the perioperative setting.

EPIDEMIOLOGY

Incidence

Major surgery is a common procedure, which has the potential to induce AKI. In the ICU setting, it is the most common contributor for AKI after sepsis [6] accounting for one in every three patients. A large retrospective study conducted in the United States

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KEY POINTS

- AKI is the fourth most common postoperative complication. It develops in roughly 10% of surgical patients, and in up to one-third after cardiac surgery.
- The management requires an individualized multicomponent approach, with hemodynamic optimization being one of the most important measure.
- Fluid overload is associated with poor outcomes. However, a recent large multicenter RCT reported that a restrictive strategy for fluid management was also harmful to the kidney function.
- Continuous monitoring of urinary oxygenation appears feasible and promising to assess the real-time effect of therapeutic interventions.
- Further research is needed to confirm the encouraging preliminary results observed with the use of angiotensin II in patients with shock and severe AKI.

between 2004 and 2011 included 3.6 million veterans among which 161 185 had major surgery hospitalizations [7]. Overall, 11.8% of the cases were complicated by postoperative AKI, among which 2.2% required renal replacement therapy (RRT). The incidence of AKI varies significantly according to the type of surgery. Indeed, according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, the incidence of AKI is estimated to be roughly 36% after cardiac surgery [8,9], 12% after thoracic surgery [7], 7–11% after orthopedic surgery [7,10], and 6–7% after major abdominal surgery [11▪▪,12]. The surgical technique also impacts on the risk of developing AKI. For example, laparoscopic procedures have been associated with a 28% reduction in postoperative AKI compared with open surgery [7].

Predictors of acute kidney injury

The most common nonmodifiable risk factors are age and preexisting chronic kidney disease. In addition, male sex, African American race, hypertension, diabetes, higher BMI, and preexisting comorbidities (i.e. congestive heart failure, lung disease, malignancy, liver disease) are independently associated with a higher risk of postoperative AKI [7]. These associations remain valid for all types of surgery. Urgent surgery has also been reported to increase the risk of AKI with an adjusted hazard ratio of 1.9 (1.5–2.3) compared with elective surgery, in a study conducted in the United States involving 57 075 patients who underwent general surgery [13].

Chronic medications also impact on the risk of AKI. In a large observational study, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptors blockers (ARBs), and diuretics were associated with a greater risk of developing AKI [ACE inhibitors or ARBs: relative risk (RR) 1.2 (1.16–1.23), diuretics: RR 1.18 (1.14–1.21)], whereas statin use slightly decreased the risk [RR: 0.96 (0.93–0.99)]. However, five recent randomized controlled trials (RCT) did not demonstrate any benefit of statins in reducing postoperative AKI [14–18].

Surgery-related factors have been mainly investigated in cardiac surgery and general surgery. Overall, complex and prolonged operations, intraoperative bleeding, and hemodynamic instability during surgery are among the most consistent contributing factors for developing AKI. In cardiac surgery, prolonged aortic cross-clamping, cardiopulmonary bypass (CPB) duration, nonpulsatile CPB, hemolysis and hemodilution have been reported to increase the risk of AKI, whereas the renoprotective effect of off-pump procedures (versus on-pump) remains controversial [19]. Among patients who underwent general surgery, patient-related factors seem more strongly associated with AKI than surgical factors. Nonetheless, intraperitoneal surgery and liver transplant surgery carry an increased risk of AKI [20] whereas epidural anesthesia might reduce this risk [21].

Finally, in the postoperative period, the main risk factors of AKI are sepsis and the occurrence of other complications such as: all types of low cardiac output states, hypotension, hypovolemia, and anastomotic leak after major abdominal surgery [19,20].

PREVENTIVE AND SUPPORTIVE STRATEGIES

Supportive management to prevent AKI is the main approach in clinical practice, as therapeutic options to treat established AKI are limited. Preventive interventions include a multicomponent approach combining early identification of high-risk patients and implementation of bundles recommended by the

Table 1. KDIGO guidelines for the prevention of acute kidney injury

Recommended measures for the prevention of AKI
Discontinuation of all nephrotoxic agents whenever possible
Optimization of volume status and hemodynamic parameters including perfusion pressure
Consideration of functional hemodynamic monitoring
Close monitoring of serum creatinine and urine output
Avoidance of hyperglycemia
Consideration of alternatives to radio contrast agents
Discontinue ACE-inhibitors and ARBs

ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blockers.

Table 2. Selected studies from the 2017–2018 literature

References	Number of patients	Design	Purpose	Main results
Myles *et al.* [11▪▪]	3000	Multicenter RCT	To compare a restrictive with a standard fluid regimen in patients undergoing major abdominal surgery.	A restrictive fluid regimen was not associated with a higher rate of DFS. The restrictive regimen was associated with a higher rate of AKI.
Semler *et al.* [22▪]	15 802	RCT	To compare balanced crystalloids with saline in ICU patients.	Balanced crystalloids rather than saline had a favorable effect on a composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction.
Self *et al.* [23▪]	13 347	RCT	To compare balanced crystalloids with saline in ED patients.	No difference in hospital-free days between treatment with balanced crystalloids and treatment with saline. Balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline.
Jaber *et al.* [24]	389	Multicenter RCT	To test the hypothesis that sodium bicarbonate infusion would improve clinical outcome in critically ill patients with severe metabolic acidaemia (pH $<$ 7.2)	Sodium bicarbonate had no effect on the primary composite outcome (i.e. mortality by day 28 or the presence of at least one organ failure at day 7). In patients with AKI, sodium bicarbonate reduced the use of RRT, the number of organ failures at day 7, and mortality at day 28.
Futier *et al.* [25▪]	298	Multicenter RCT	To evaluate whether an individualized blood pressure management strategy could reduce postoperative organ dysfunction.	Individualized blood pressure management reduced the risk of postoperative organ dysfunction.

AKI, acute kidney injury; DFS, disability-free survival; ED, emergency department; RCT, randomized controlled trial.

KDIGO guidelines (Table 1). Hemodynamic management is one of the most important measure to optimize renal perfusion and tissue oxygen delivery, using protocol-based administration of intravenous fluids and vasopressors (Table 2).

Early identification of high-risk patients

Two recent studies have recently reported the performances of cell cycle arrest biomarkers to identify surgical patients at high-risk of AKI who may benefit from KDIGO guidelines implementation to reduce the incidence of postoperative AKI [26,27]. Meersch *et al.* [26] randomized 276 cardiac-surgery patients with a urinary [TIMP-2]·[IGFBP7] greater than 0.3 to either intervention arm (implementation of KDIGO guidelines) or standard care and showed an absolute risk reduction of AKI within 72 h of 16.6% [95% confidence interval (CI) 5.5–27.9%] in the intervention arm. In another study, Göcze *et al.* [27] applied a similar protocol to 121 patients who underwent major abdominal surgery and reported a reduced incidence of AKI from 48% in the standard group to 27.1% in the intervention group. However, none of these two studies reported a decreased incidence of RRT, in-hospital mortality, or major adverse kidney events. Although interesting and promising, these results need to be confirmed by further studies before using these biomarkers for risk stratification and interventions in clinical practice.

Ischemic preconditioning

Remote ischemic preconditioning by cuff inflation induces a short period of blood deprivation followed by a period of reperfusion. This method has been tested as a potential mean to protect kidneys from ischemia reperfusion injury. RCTs have reported conflicting results and a recent meta-analysis concluded that remote ischemic preconditioning led to little or no difference in serum creatinine levels, incidence of AKI, need for dialysis, and mortality [28].

Fluid management

Administration of intravenous fluids is one of the first responses to hypotension or oliguria [29,30]. However, the optimal amount, timing, and type of fluid, as well as the parameters used to guide fluid administration remain a matter of debate.

The main objective of fluid administration in surgical patients is to treat hypovolemia, in order to avoid its potential side-effects, including AKI. The use of intraoperative hemodynamic monitoring to

guide interventions (i.e. fluids, vasopressors and inotropes administration) aiming at keeping the cardiac index within the normal range and optimizing oxygen delivery has been shown to reduce hemodynamic instability and decrease the risk of postoperative AKI, regardless the type of technological device implemented [31–34]. Such monitoring devices are also useful to avoid unnecessary fluid administration, as numerous observational studies have reported deleterious effects associated with fluid overload in the perioperative period, such as increased mortality and worsening of renal function [35–37]. Therefore, recent consensus statements had recommended a restrictive approach to fluid strategies, aiming zero-balance to reduce complications in the perioperative period [38–40]. However, a recent pivotal large multicenter randomized trial has contradicted this approach. In this study, 3000 patients who had major abdominal surgery were randomized to a restrictive or liberal strategy for fluid therapy [11▪▪]. The median amount of fluid administered 24 h after surgery in the liberal and restrictive groups were 6.1 l and 3.7 l, respectively. Although there was no difference in mortality between the two groups, patients randomized in the restrictive fluid therapy developed more AKI (8.6 versus 5.0%, $P < 0.001$), need for RRT (0.9 versus 0.3%, $P = 0.048$), and surgical-site infections (16.5% versus 13.3%, $P = 0.02$) than patients in the liberal strategy. Thus, these results support the theory of a U-shaped relationship between the amount of fluids administered and the physiological consequences, with both too liberal and too restrictive strategies being harmful to the kidneys.

The type of fluids may also be important. Crystalloids are the most commonly prescribed fluids in the perioperative setting. There is a theoretical advantage of using buffered solutions rather than isotonic saline to maintain body's acid-base status and avoid hyperchloremia, which might contribute to the development of AKI [41,42]. A meta-analysis of 18 RCTs published in 2017 concluded that although buffered solutions reduced postoperative hyperchloremia, this biochemical effect was not associated a reduced risk of AKI compared with nonbuffered solutions [43]. However, two recent RCTs published in 2018, which found a lower incidence of major adverse kidney events (a composite outcome of death from any cause, new RRT, or persistent renal dysfunction within 30 days after randomization) with balanced crystalloids compared with isotonic saline were not included in this meta-analysis [22▪,23▪]. These two trials were conducted in the emergency department and in the ICU. Further research is needed to confirm these results in the perioperative environment. Colloid solutions are another common option for fluid resuscitation. However, there is no evidence from RCTs that colloids reduce mortality after surgery compared with crystalloid solutions [44]. Furthermore, hydroxyethyl starches are no longer recommended for fluid resuscitation in the ICU environment because they are associated with an increased risk of AKI [44,45], and remain a matter of debate in other settings [46,47]. Albumin has interesting physiological properties such as being the main molecules carrier with buffered and antioxidant properties, and a long half-life. However, data from two large RCTs did not demonstrate any benefit in survival, risk of AKI, and use of RRT, compared with crystalloid solutions [48,49]. Sodium bicarbonate has been compared with isotonic saline in cardiac surgery patients to prevent AKI [50]. In this RCT, the use of bicarbonate was associated with a higher incidence of AKI compared with isotonic saline (47.7 versus 36.4%, $P = 0.03$). Moreover, this study was stopped early because there was an increased mortality in patients receiving sodium bicarbonate (6.3 versus 1.7%, $P = 0.03$). Thus, the use of sodium bicarbonate to prevent AKI cannot be recommended. However, a recent RCT (including more than 40% of surgical patients) compared sodium bicarbonate to other solutions in ICU patients with severe metabolic acidosis ($pH < 7.2$) [24]. The primary outcome was a composite of death from any cause by day 28 and the presence of at least one organ failure at day 7, and was not different in the two groups (71 versus 66%, $P = 0.24$). However, in the predefined subgroup of patients who had AKI stage 2 or 3 according to the AKIN classification, patients treated by sodium bicarbonate had a 22.2% reduction in the use of RRT, less organ failures at day 7, and a lower mortality at day 28 compared with patients treated with other solutions. Although preliminary, these suggest that bicarbonate solutions might be beneficial in patients with established AKI and severe metabolic acidosis.

Vasopressors

Vasopressors are commonly used in the perioperative setting when fluids failed to restore adequate blood pressure. Noradrenaline is recommended as the first-line agent in vasodilatory states [51]. Vasopressin and terlipressin may be alternatives [52–55], although their benefit on kidney function is not demonstrated. More recently, promising results have been reported with the use of angiotensin II in experimental and clinical studies [56,57]. In a post hoc analysis of a RCT, angiotensin II has been reported to improve day-28 survival and RRT liberation in patients with vasodilatory shock and AKI requiring RRT [57].

Personalized blood pressure strategy

Hemodynamic instability is common during and after major surgery. However, there is no consensus on the optimal target for blood pressure and guidelines for noncardiac surgery recommend individualizing management for patients with comorbidities [58]. In a RCT comparing two different thresholds of blood pressure in patients with septic shock (65–70 versus 80–85mmHg), patients with a history of hypertension randomized in the high-target group had lower incidences of doubling plasma creatinine (52 versus 38.9%, $P = 0.02$) and RRT (42.2 versus 31.7%, $P = 0.04$) than patients randomized in the low-target group [59]. The INPRESS study is a multicenter RCT, which evaluated whether an individualized blood pressure management strategy could reduce postoperative organ dysfunction among patients at moderate-to-high risk of AKI undergoing major surgery [25▪]. Among the 298 patients enrolled, 149 were randomized in the standard group and 149 in the individualized treatment strategy. This individualized strategy aimed to achieve a SBP within 10% of the patient's resting reference. Such approach reduced the risk of postoperative organ dysfunction by day 7 after surgery compared with standard blood pressure management (38.1 versus 51.7%, $P = 0.02$).

Renal replacement therapy

AKI requiring RRT occurs in 0.5–5% of patients after major surgery [11▪▪,19] and is associated with poor outcomes [60–62]. However, specific data on surgical patients are limited. Combes *et al.* [60] conducted a multicenter RCT to test the hypothesis that early initiation of high-volume hemofiltration (HVHF) in cardiac surgery patients with shock would improve outcomes compared with standard care. In this study, 224 patients were randomized to receive early HVHF (80 ml/kg/h for 48 h) or standard care. The primary outcome was day-30 mortality and there was no difference between the two groups (36 versus 36%, $P = 1.00$). Moreover, ICU, hospital, and day-90 mortality rates did not differ, as well as renal recovery. In another conducted in Taiwan, Shiao *et al.* reported the outcome of 98 patients who underwent RRT after major abdominal surgery [61]. Hospital mortality occurred in 58.2% of the patients and late initiation of RRT (defined as starting RRT at AKI stage I or F of the RIFLE criteria) was identified as an independent predictor of mortality. However, the observational design of the study precludes any definite conclusion. Therefore, the KDIGO guidelines on modalities and dose of RRT should be used for patients undergoing major surgery [63]. The timing of RRT in ICU patients has been recently investigated by two RCTs with conflicting results [64,65]. The multicenter AKIKI trial compared two different timings of RRT initiation (early versus late) in 620 patients with AKI stage 3 and found no difference in day-90 mortality between the two strategies [64]. On the other hand, the single-center ELAIN trial randomized 231 patients and found a better survival with early initiation (AKI stage 2) than late initiation (AKI stage 3). Thus, the ideal timing of RRT initiation is yet to be determined.

ONGOING RESEARCH

Urinary oxygenation

Hypoxia of the renal medulla appears to be an important contributor of AKI in cardiac surgery patients [19,66]. Continuous monitoring of urinary PO_2 through a fiber optic probe placed in the bladder catheter is a reliable surrogate of renal medullary PO_2 in animal models [67,68]. Zhu *et al.* [69▪] enrolled 65 patients in a pilot study to test the hypothesis that urinary hypoxia during CPB was a predictor of AKI. They found that urinary PO_2 fell during the operation and that low intraoperative urinary PO_2 was an independent predictor of postoperative AKI. These interesting findings suggest that urinary PO_2 may be a real-time biomarker of renal physiology, which might be useful to assess immediately the effect of therapeutic interventions during surgery.

Nitric oxide

Hemolysis during prolonged CPB releases oxyhemoglobin and promotes AKI through a combination of mechanisms such as intrarenal oxidative reactions and vasoconstriction. NO oxidizes oxyhemoglobin into methemoglobin, and therefore, potentially prevents organ injury. Lei *et al.* [70] have randomized 244 cardiac surgery patients to receive either NO or nitrogen via the gas exchanger during CPB and by inhalation for 24 h postoperatively. Patients randomized in the NO group had a lower incidence of postoperative AKI than those in the nitrogen group (50 versus 64%, $P = 0.01$). Moreover, they had lower rates of stage 3 chronic kidney disease (CKD) at day 90 (21 versus 33%, $P = 0.02$) and 1 year (18 versus 31%, $P = 0.01$). Further studies are required to confirm this single-center experience. However, NO therapy seems to be a promising area of research to sustainably reduce renal dysfunction after cardiac surgery.

CONCLUSION

In conclusion, AKI remains a frequent and severe complication after major surgery, independently

associated with increased short-term and long-term mortality, and higher risk of developing CKD. Identifying high-risk patients and implementing personalized preventive strategies can decrease the incidence of postoperative AKI. In clinical practice, hemodynamic monitoring and protocol-based administration of fluids and vasopressors during and after surgery are the most important measures to prevent hypotension and hypovolemia, which are the main modifiable contributors of AKI. Careful attention should be paid to avoid the side-effects of both fluid accumulation and hypoperfusion. Further research is needed to confirm whether urinary PO_2, nitric oxide, and angiotensin II will help reducing postoperative AKI and improving patients' outcomes.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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