
Protecting the Beans:
Perioperative Acute Kidney Injury
Acute kidney injury is a common occurrence in hospitalized patients which…
…impacts 12% of hospital admissions.[1]
…costs $12 billion per year in the US alone.
… ↑ length of stay by an average of 3 days.
Contributing factors
Chronic kidney disease
Inflammation
Damage associated molecular patterns (i.e. myoglobin)
Nephrotoxins
Urinary obstruction
Risk reduction
Maintain: Euvolemia, perfusion pressure and normoglycemia
Monitor: Urine output, creatinine and hemodynamic status
Normal saline
Nephro-toxins
Avoid normal saline and reduce exposure to other nephrotoxins for all patients.

Among the many complications that can impact a hospitalized patient, acute kidney injury stands out as one of the most prevalent and expensive, and is associated with worse outcomes in both the short and long term. While this complication is multifactorial and not consistently preventable, there are a number of risk factors for the development of acute kidney injury that can potentially be modified. In this infographic, we review the most common factors associated with acute kidney injury in perioperative care, as well as a bundle of interventions that have been suggested to be beneficial in the care of these patients.

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1. Zarbock A, Koyner JL, Hoste EAJ, Kellum JA. Update on perioperative acute kidney injury. *Anesth Analg*. 2018;127:1236–1245.

Update on Perioperative Acute Kidney Injury

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Acute kidney injury (AKI) in the perioperative period is a common complication and is associated with increased morbidity and mortality. A standard definition and staging system for AKI has been developed, incorporating a reduction of the urine output and/or an increase of serum creatinine. Novel biomarkers may detect kidney damage in the absence of a change in function and can also predict the development of AKI. Several specific considerations for AKI risk are important in surgical patients. The surgery, especially major and emergency procedures in critically ill patients, may cause AKI. In addition, certain comorbidities, such as chronic kidney disease and chronic heart failure, are important risk factors for AKI. Diuretics, contrast agents, and nephrotoxic drugs are commonly used in the perioperative period and may result in a significant amount of in-hospital AKI. Before and during surgery, anesthetists are supposed to optimize the patient, including preventing and treating a hypovolemia and correcting an anemia. Intraoperative episodes of hypotension have to be avoided because even short periods of hypotension are associated with an increased risk of AKI. During the intraoperative period, urine output might be reduced in the absence of kidney injury or the presence of kidney injury with or without fluid responsiveness. Therefore, fluids should be used carefully to avoid hypovolemia and hypervolemia. The Kidney Disease: Improving Global Outcomes guidelines suggest implementing preventive strategies in high-risk patients, which include optimization of hemodynamics, restoration of the circulating volume, institution of functional hemodynamic monitoring, and avoidance of nephrotoxic agents and hyperglycemia. Two recently published studies found that implementing this bundle in high-risk patients reduced the occurrence of AKI in the perioperative period. In addition, the application of remote ischemic preconditioning has been studied to potentially reduce the incidence of perioperative AKI. This review discusses the epidemiology and pathophysiology of surgery-associated AKI, highlights the importance of intraoperative oliguria, and emphasizes potential preventive strategies. (Anesth Analg XXX;XXX:00–00)

Acute kidney injury (AKI) is an abrupt decline of the kidney function that occurs within a few hours or days. The term AKI appreciates that smaller declines in kidney function that do not result in overt organ failure are still of clinical relevance and are associated with increased morbidity and mortality.[1] AKI is a possible reversible syndrome that can develop in patients with and without comorbidities. Sepsis, major surgery, and various drugs are the leading causes of AKI.[1] Although AKI is a common complication in the perioperative period, it remains an underdiagnosed clinical condition. The consensus criteria that were developed recently have helped to attract more attention toward this serious clinical syndrome.[2] Based on the new definition, AKI is now being diagnosed more frequently over the last 2 decades. The new consensus definition is based exclusively on urine output and/or serum creatinine (SCr), thereby classifying different AKI severity stages (Table 1).[2] Since the advent of standard criteria for AKI culminating in the Kidney Disease: Improving Global Outcomes (KDIGO) criteria,[2] there has been an increased appreciation for AKI in terms of both its frequency and impact on survival. Furthermore, even mild changes in kidney function, as assessed by SCr, urine output, or both, seem to be associated with short- and long-term adverse outcomes. However, both functional markers have several limitations, including the inability to allow an early diagnosis. Thus, there is a need for an early identification of high-risk patients to immediately initiate preemptive treatment.

During the 2018 IARS meeting in Chicago, we had an *Anesthesia & Analgesia*-sponsored symposium dealing with the most important aspects of perioperative AKI, including epidemiology and pathophysiology of surgery-associated AKI (SA-AKI), importance of intraoperative oliguria, and potential preventive strategies. This review summarizes the talks and covers these aspects.

EPIDEMIOLOGY

AKI is a frequently occurring complication during a hospital stay. In the United States, AKI is estimated to occur in 12% of hospital admissions, affecting 2.2 million hospitalized people per year. This comes with a death toll of 220,000 patients per year, an increase of the length of hospital stay by 3 days, and an estimated excess in hospital costs of $12 billion per year.[3] The 30-day mortality rate for patients with AKI is higher than breast cancer, prostate cancer, heart

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failure, and diabetes combined. AKI is also closely interconnected with chronic kidney disease (CKD): patients with AKI are at greater risk for developing CKD, and vice versa, patients with CKD are at greater risk for developing AKI.[4] Both AKI and CKD are now regarded as part of a syndrome where each is at the opposite end of the spectrum of kidney disease. Given all these elements, kidney disease may now be regarded as a significant global health burden.[5,6]

In patients in the intensive care unit (ICU), major surgery is the second most frequent reported etiology of AKI (SA-AKI).

Table 1. The Kidney Disease: Improving Global Outcomes, Diagnosis, and Grading System for AKI

Stage	Serum Creatinine	Urine Output
1	≥1.5–1.9 times baseline or >.3 mg/dL (26.5 μmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	≥2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	≥3.0 times baseline or Increase of serum creatinine to ≥4.0 mg/dL (353.6 μmol/L) or RRT or In patients <18 y, decrease of eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥24 h or Anuria for ≥12 h

(1) AKI is defined by either an increase of serum creatinine or a reduced urine output: In an increase of serum creatinine ≥0.3 mg/dL (26.5 μmol/L) within 48 h or an increase of serum creatinine by ≥1.5-fold above baseline, known or assumed to have occurred within 7 days, or urine volume <0.5 mL/kg/h for 6 h. (2) AKI severity is staged by the worst of either serum creatinine changes or reduced urine output.

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

Definition of AKI

AKI is defined and staged into 3 severity stages by a combination of either an increase of SCr or a period of oliguria (Table 1).[2] Rapid reversal of AKI is defined by a duration of ≤48 hours and acute kidney disease by an episode of AKI lasting between 7 and 90 days.[7] Limitations of this definition include the use of a baseline SCr concentration (Table 2). In elective surgery, this may be assessed by a preoperative blood draw. However, in emergency surgery or trauma, a baseline creatinine value that represents recent kidney function is not always available. Back calculation with the modification of diet in renal disease equation for the assessment of estimated glomerular filtration rate (GFR) can be used to estimate baseline SCr for patients without CKD.[8] This back-calculated estimate of baseline SCr may overestimate or underestimate AKI stage 1, but it is unlikely to misclassify stage 2 or 3.[9] A true decline in kidney function may be underestimated as an increase of SCr may be blunted by decreased production of creatinine in critically ill patients or dilution as a consequence of volume resuscitation.

Epidemiology of SA-AKI

In the worldwide multicenter AKI-EPI study, the incidence of AKI within the first week after ICU admission was 52% in patients who were admitted after scheduled surgery and 56% after emergency surgery. This figure compared to 62% of patients in the medical ICU and an overall incidence of 57%.[10]

Given the heterogeneous and multifactorial etiology of AKI and the wide variation in patient-related risk factors, incidence estimates vary widely. In cardiac surgery, recent meta-analyses showed that AKI had a median rate of 22%, with predominantly low severity AKI stage 1 and use of renal replacement therapy (RRT) in 3% of patients.[11]

Table 2. Strategies to Diagnose and Prevent/Treat AKI

Tools and Measures	Notes	Reference
Diagnostic tools		
Serum creatinine and urine output	Both parameters are used to diagnose and stage AKI, but these functional biomarkers have certain limitations. Serum creatinine has a low sensitivity, whereas urine output has a low specificity.	2
Biomarkers	Biomarkers can detect kidney stress and damage. Several studies have shown that they can predict the development of AKI. The FDA-approved biomarkers TIMP2*IGFBP7 indicate kidney stress in advance of AKI.	78, 79
Furosemide stress test	The test can predict disease progression and adverse outcome in the setting of early AKI.	67–70
Preventive measures		
Preventing hypotension	Prolonged episodes of hypotension in the intraoperative period may induce an AKI.	83–85
Avoiding 0.9% saline	Large amounts of 0.9% saline leads to hyperchloremic acidosis and renal vasoconstriction and increase the risk of AKI.	89–91
RIPC	Several clinical trials showed that RIPC can reduce the occurrence of AKI after surgery.	96, 97
KDIGO bundle (discontinue all nephrotoxic agents when possible, ensure volume status and perfusion pressure, consider functional hemodynamic monitoring, monitor serum creatinine and urine output, avoid hyperglycemia, and consider alternatives to radiocontrast procedures)	Two studies demonstrated that the application of the KDIGO bundle in high-risk patients can prevent the occurrence of AKI in the perioperative period.	100, 101
Therapeutic measures		
RRT	No specific therapies are available to treat AKI. RRT is the only supportive measure for patients with severe AKI.	

Abbreviations: AKI, acute kidney injury; FDA, Food and Drug Administration; IGFBP7, insulin-like growth factor-binding protein 7; KDIGO, Kidney Disease: Improving Global Outcomes; RIPC, remote ischemic preconditioning; RRT, renal replacement therapy; TIMP2, tissue inhibitor of metalloproteinases 2.

In major abdominal surgery, the reported incidence varies from 6.7% to 39.3%.[12]

Several large administrative databases show an important increase of the incidence of AKI. This finding may be explained by better administrative coding and a lower threshold for the use of RRT. However, given the changing profile of the hospitalized patient who is getting older, is more frail, and has more comorbidities, this is most likely also reflecting a true increase.[13–16]

Patient Outcomes

SA-AKI is associated with worse patient outcomes, such as increased length of stay in the ICU and hospital and hospital mortality. This association remains even after adjustment for covariates, with a stepwise increase of mortality risk with increasing severity stage of AKI.[10,17,18] This may be explained by the detrimental effects of AKI on other organs predominately mediated by inflammatory changes.[19] AKI is also associated with worse long-term patient outcomes. In a study on patients with AKI treated with RRT, 5-year mortality of 90-day survivors was 30%.[20] Similar to the hospital survival, there is also a stepwise decrease of long-term survival with increasing severity stages of AKI.[21–25]

While acute effects of AKI on patient outcomes can be explained by effects on distant organ function, the effects on long-term outcomes are more difficult to explain. A large proportion of AKI survivors have evidence of CKD, as shown by a decreased estimated GFR or proteinuria.[20] This effect is even more pronounced in patients who already had CKD before the development of AKI. Several large cohort studies have shown that AKI survivors have an increased risk for cardiovascular disease such as myocardial infarction, heart failure, and stroke.[26–28]

PATHOPHYSIOLOGY

AKI is a nonspecific clinical syndrome defined by a rapid loss of GFR.[29,30] Even perioperative AKI includes multiple different syndromes (Figure 1), and proper therapy can vary widely.

To support clinical diagnosis and facilitate studies, AKI is classified based on specific clinical and laboratory criteria.[2] However, AKI is a clinical diagnosis, and these criteria do not define it in the same way that electrocardiographic changes and troponin do not define myocardial infarction. Azotemia and oliguria are indicative of pathology as well as of normal responses of the kidney to extracellular volume depletion or a decreased renal blood flow. In fact, a "normal" urine output and GFR in the face of volume depletion would actually indicate renal dysfunction. Thus, changes in urine output and GFR are neither necessary nor sufficient for the diagnosis of renal pathology.[31] Still, they serve as the backbone for our existing diagnostic criteria[2]—checklists or similar tools may help in difficult cases.[32] Healthy individuals, particularly younger adults, have substantial renal reserve[33,34] and can lose more than half their renal function before SCr changes.

Pathogenesis of Perioperative AKI

The traditional taxonomy of AKI based on pseudo-anatomic locations (pre, intra, and post) in reference to the kidney is overly simplistic and has given way to specific "AKI paradigms,"[29] including hepatorenal,[35] cardiorenal,[11] nephrotoxic,[36] sepsis-associated,[37] and urinary tract obstruction. These syndromes all have unique pathophysiologies and treatments and may also have different molecular signatures.[38] Surgery can injure the kidney in a number of ways, and surgical patients may be exposed to a number of injurious stimuli in the perioperative period (Figure 1). For treatment, these various syndromes need to be considered separately rather than lumped together as 1 disease. At times, therapies will be diametrically opposed.[30] For example, will a patient with AKI benefit from fluid administration, diuresis, or neither? The answer depends on whether the patient has cardiorenal physiology from acute decompensated heart failure where the answer will usually be diuresis or septic shock and where judicious use of fluids is required (but further fluid use will not be helpful) or nephrotoxic AKI where both fluids and diuretics may be harmful. Perioperative AKI syndromes include hemodynamic-, nephrotoxic-, damage-associated molecular pattern (DAMP)-induced inflammation and obstruction (Figure 1).[29]

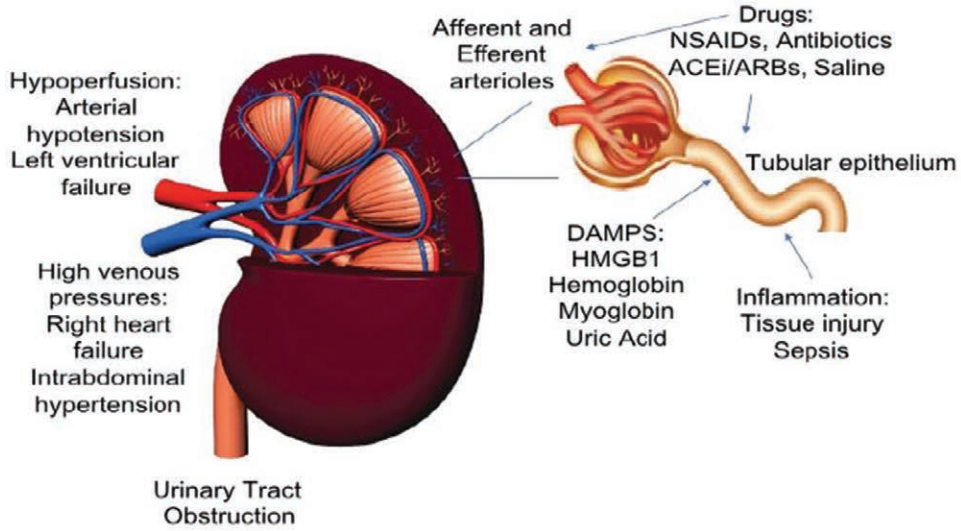

Figure 1. Perioperative AKI syndromes. Major mechanisms of acute kidney injury in the perioperative setting. ACEi indicates angiotensin-converting-enzyme inhibitor; AKI, acute kidney injury; ARB, Angiotensin II receptor blockers; HMGB1, High-Mobility-Group-Protein B1; NSAID, nonsteroidal anti-inflammatory drug.

Hemodynamic-Mediated AKI

Surgery can result in hypovolemia, anesthetics can cause venodilation, and positive pressure ventilation can impair venous return to heart—all 3 reducing preload. Anesthetics can also reduce arterial tone, further compromising perfusion pressure. Clinicians are usually well conditioned to responding to these threats. However, right-sided hemodynamics are critical as well. In cardiac surgery, the right heart may be compromised from cardioplegia. In thoracic surgery, high pleural pressure may increase venous "back pressure" on various organs, including the liver and kidneys. In abdominal surgery, the high pressure may be in the abdomen. In all of these cases, the high venous pressure can injure the kidney by causing congestion within an organ that cannot expand. It may also compromise perfusion, particularly if arterial blood pressure is not increased to account for the loss of perfusion pressure. Therefore, excessive intravenous fluids may contribute to AKI, but overly restrictive fluid management may also be injurious to the kidney.[39]

DAMP-Induced AKI

Another consequence of the hemodynamic alterations is the effect of reduced tissue perfusion in remote organs (eg, muscle). Various molecules are released during ischemia–reperfusion, including myoglobin, uric acid, and High-Mobility-Group-Protein B1 (HMGB1). These molecules are in a class of DAMPs that can signal through pattern recognition receptors including Toll-like receptors such as Toll-like receptor 4.[37] Tissue injury because of trauma or surgery itself can also release DAMPs into the circulation. Indeed, even mild ischemia–reperfusion of the arm can illicit the release of HMGB1 into the circulation with the triggering of a stress response in the kidney.[40] Cardiac surgery is associated with AKI, and efforts such as avoiding cardiopulmonary bypass appear to reduce the risk of AKI. In a trial of nearly 3000 patients, cardiac surgery "off-pump" reduced the risk of AKI (17.5% vs 20.8%; relative risk, 0.83; 95% confidence interval [CI], 0.72–0.97; $P = .01$) compared to standard technique using cardiopulmonary bypass.[41] In addition to the hemodynamic effects of cardiopulmonary bypass, there is often hemolysis, and plasma-free hemoglobin can also function as a DAMP.

Inflammation

Surgery and the healing process that follows is a well-known cause of inflammation. Inflammatory mediators such as tumor necrosis factor-α as well as activation of circulating immune effector cells can injure the kidney. Cardiopulmonary bypass also induces inflammation. Sepsis produces profound systemic inflammation and is also associated with the release of pathogen-associated molecular patterns that signal through some of the same receptors.[37]

Nephrotoxic AKI

Nephrotoxic AKI is a particularly prevalent condition in this population, and it appears quite amenable to practice change.[42] Goldstein[43] at Cincinnati Children's Hospital has spearheaded efforts to reduce nephrotoxicity by identifying patients electronically. Antibiotics can be nephrotoxic in both direct (eg, aminoglycosides) and indirect ways. Allergic interstitial nephritis, for example, may occur even in patients who do not manifest other signs of allergy. Antibiotics also kill bacteria, and some release more bacterial cell products (eg, endotoxin) into the circulation than others. These pathogen-associated molecular patterns can then directly injure the kidney or contribute to systemic inflammation.[44] Certain fluids may also contribute to AKI.[45,46] Hydroxyethyl starch has been linked to AKI and decreased survival in patients with severe sepsis.[45] Although these results were not confirmed in a larger trial,[47] the exposure was less, and there was still some evidence of renal toxicity, albeit only in the rates of acute RRT. Saline increases rates of major adverse kidney events (death, dialysis, or persistent renal dysfunction) in both critically ill and noncritically ill patients.[48,49]

Urinary Tract Obstruction

Colorectal, urological, and gynecological surgery are often associated with urinary retention, although normally not complete obstruction. Drug-associated urinary retention is also a risk. Injury to the ureters is always a potential complication, and unilateral injury can be easily missed. Malfunctioning or misplacement of the Foley catheter or clogging of the catheter can also result in obstruction.

OLIGURIA IN THE PERIOPERATIVE SETTING

Oliguria by itself may be an appropriate response in patients with intravascular volume depletion or hypovolemia. In these patients, adequate volume expansion with the appropriate crystalloid (nonhyperchloremic) or colloid should reverse the process. However, oliguria can also be maladaptive in the settings of congestive heart failure, end-stage liver disease with ascites, and acute tubular necrosis/AKI with volume overload. In these settings, the kidney is not able to provide the appropriate natriuresis perhaps due to renal congestion in the setting of increased right-sided vascular pressures or activity of antidiuretic hormone (ADH). Determining the underlying source of oliguria can perhaps lead to improved volume status and eventually improved kidney function.

In prior investigations, isolated urine output–based AKI has been shown to be more common but associated with less severe adverse outcomes than isolated SCr-based AKI.[50–53] In a retrospective cohort study looking at adults without end-stage renal disease who underwent major noncardiac surgery, 4229 subjects had sufficient creatinine and urine output (UOP) measurements for analysis.[50] Adding UOP to the SCr-based AKI increased the incidence of AKI from 8% to 60%. In adjusted analyses, stage 3 UOP-based AKI was associated with a 2.84 (1.41–5.70) increased odds of 30-day mortality compared to those with no AKI, but this was less compared to those with stage 3 SCr-based AKI (5.00 [1.65–15.17]) and those with combined UOP- and SCr-based stage 3 (7.85 [2.76–22.33]). However, Mizota et al[54] published a single-center study demonstrating that in 320 living donors for liver transplantation, 12% had SCr-based AKI, 22% had UOP changes, and 28% had AKI by both criteria. They demonstrated significantly longer ICU and hospital stays in those with isolated UOP-based AKI compared to SCr-based AKI. These studies highlight that oliguria is common in the perioperative period and is associated with adverse outcomes.

Oliguria is usually thought to be due to intravascular volume depletion or prolonged systemic hypoperfusion, both of which are believed to lead to reduced renal perfusion and result in decreased filtered load and urine production. However, oliguria can also occur in the setting of ADH release as well as in the presence of increased aldosterone secretion.[55,56] In the perioperative setting, ADH release can come from a variety of nonrenal stimuli, including pain, nausea, and type of surgery (neurological or otherwise).[56,57] Regardless of its source, oliguria in the ICU has been associated with increased mortality.[51,52,58] In a systematic review and meta-analysis, Prowle and coworkers[59] investigated the incidence of perioperative AKI following major abdominal surgery. While they did not separate UOP-based AKI from SCr-based AKI, they demonstrated that AKI occurred in 13.4% of patients (from 8 studies and 82.514 patients) and was associated with a 12.6-fold (95% CI, 6.8–23.4) increased relative risk of short-term perioperative mortality.[59]

Intraoperative Fluid Balance and UOP

The impact of fluid management on AKI and UOP in the perioperative setting has been investigated. The prevailing thought is that volume expansion could lead to improved hemodynamics and renal perfusion and consequently more UOP and perhaps less AKI. Historically, in 2 separate randomized controlled trials investigating fluid-restrictive versus fluid-liberal intravenous fluid strategies, evidence showed that fluid-liberal strategies led to longer hospital stays and more perioperative complications.[60,61] However, these studies neither demonstrated a difference in AKI rates nor reported UOP-based outcomes.

More recently, 2 small randomized controlled trials demonstrated no difference in intraoperative UOP in patients randomized to liberal (8–10 mL/kg/h) versus restrictive (2–4 mL/kg/h) fluid strategies.[62,63] Both these separate studies in 107 patients undergoing laparoscopic bariatric surgeries and 102 patients undergoing video-assisted thoracoscopic surgery showed no difference in intraoperative UOP and postoperative AKI rates in patients receiving lactated ringers.[62,63] Some have hypothesized that the lack of impact on UOP and AKI outcomes are due to altered distribution and elimination of intravenous fluids in the setting of laparoscopic procedures. These alterations lead to rapid fluid administration (eg, as a part of fluid-liberal strategies) and may preferentially be less responsive to diuretics as well as lead to increased peripheral edema.[64]

However, the results of these smaller studies were not substantiated in a recent large prospective multicenter international trial looking at 3000 patients who had an increased risk for complications undergoing major abdominal surgery and who were randomized to receive either a fluid-liberal or fluid-restrictive strategy in the first 24 hours after surgery (Restrictive Versus Liberal Fluid Therapy for Major Abdominal Surgery trial).[39] A total of 1490 patients in the restrictive arm received a median (interquartile range) of 3.7 (2.9–4.9) L compared to 6.1 (5.0–7.4) L in the liberal group, and this led to increased rates of intraoperative oliguria and lower intraoperative UOP in the restrictive arm (250 [144–440] vs 350 [200–600]; $P < .001$). In addition to impacting perioperative UOP, there was an increased rate of KDIGO SCr-based AKI in the restrictive group (26.4% vs 19.0% in the liberal group; $P < .001$). More specifically, patients in the restrictive group were twice as likely to develop stage 2 or 3 AKI compared to those in the liberal arm (odds ratio [OR], 2.02; 95% CI, 1.43–2.85; $P < .001$). Finally, 0.9% of the restrictive group required RRT compared to 0.3% of the liberal group (hazard ratio, 3.27; 95% CI, 1.01–13.8; $P = .048$).[39] These emerging data point to the potential dangers of volume restriction on perioperative kidney function and may help guide future clinicians in terms of striking the balance of finding the optimal volume status.

Prior to this large-scale investigation, there had only been a handful of retrospective cohort studies that published data on the interplay between intraoperative UOP and postoperative AKI.[65,66] Mizota et al[66] published a single-center, retrospective cohort study of 3560 patients who underwent major abdominal surgery and investigated several intraoperative oliguria thresholds to determine their association with postoperative AKI. After excluding all patients who received intraoperative diuretics (furosemide, human atrial natriuretic peptide, or mannitol), they demonstrated that patients with UOP between 0.3 and 0.5 mL/kg/h did not have an increased risk of postoperative AKI (adjusted OR, 1.37; 95% CI, 0.88–2.13; $P = .160$). However, an intraoperative UOP < 0.3 mL/kg/h (which occurred in 11.3% of the cohort) was independently associated with a 2.65-fold (1.77- to 3.97-fold) increase odds of postoperative AKI ($P < .001$).[66] This effect was present across a variety of subgroups, including those who did and did not receive laparoscopic surgeries and those with and without 10 mL/kg of intraoperative blood loss and across several types of surgeries. While these data/novel cutoffs need to be further validated (eg, in other cohorts like the aforementioned Restrictive Versus Liberal Fluid Therapy for Major Abdominal Surgery trial), it remains to be seen if 0.3 mL/kg/h is a better threshold for the prediction of postoperative AKI and other adverse outcomes. However, it is line with emerging data that demonstrate that the intensive monitoring of UOP in hospitalized patients (defined as no gaps in urine output data for >3 hours) leads to improved AKI detection, decreased incidence of fluid overload, and improved survival in those who develop AKI.[51] Thus, we anticipate future studies to attempt to balance the benefits of a postoperative fluid-liberal strategy with the risk of volume overload and to determine the optimal resuscitation strategy to prevent postoperative oliguria and the resultant AKI.

Furosemide Stress Test

The majority of this prior work has focused on fluid balance and monitoring urine output during surgeries to predict AKI. More recently, several studies have investigated the kidney's UOP response to a protocoled dose of furosemide to predict adverse outcomes in the setting of early AKI (furosemide stress test).[67–70] Furosemide is an ideal agent for interrogating renal function because it requires several aspects of the nephron to be intact. On delivery to the kidney through systemic circulation, furosemide is transported across from the basolateral side of the proximal tubule through the tubular cells and into the urinary space through

the organic anion transporters.[71] After that it requires a functioning thick ascending limb of the loop of Henle, where it acts on the sodium, potassium 2 chloride channel, resulting in increased sodium excretion and increased urine output. Finally, it requires an intact distal nephron and collecting ducts to maintain the diuresis.

Initially, Chawla et al[67] demonstrated that the 2-hour cumulative UOP following 1 or 1.5 mg/kg of intravenous furosemide in patients in euvolemic or hypervolemic ICU with stage 1 or 2 AKI provided an area under the curve (AUC; SE) of 0.87 (0.09) for the prediction of progression to stage 3 AKI. A cutoff of <200 mL of urine in the first 2 hours following the furosemide challenge provided 87% sensitivity and 84% specificity for the progression to stage 3. While the finding of this study has been replicated in other similar mixed-medical patients in the surgical ICU, the authors of 2 other studies used a modified retrospective version of this concept to investigate the ability of furosemide responsiveness to predict AKI outcomes.[69,72] In a retrospective investigation of infants undergoing cardiac surgery, they demonstrated that even after correcting for the impact of fluid balance on SCr that decreased UOP following a furosemide challenge predicted postoperative AKI with an AUC of 0.74 at 2 hours but 0.77 at 6 hours.[72] This 6-hour time point is similar to findings published by McMahon et al[70] who demonstrated the 6-hour UOP following a single dose of 100 mg of intravenous furosemide provided an AUC of 0.85 for the development of delayed graft function in adults undergoing deceased donor kidney transplantation. Thus, while there is a wealth of data accumulating about the prognostic benefits of the furosemide stress test, it still requires further prospective investigation across several types of surgical patients.

PREVENTION OF AKI

Urine output and SCr, 2 functional biomarkers, are changing very late during the development of AKI and have certain limitations (Table 2). Although recently published evidence demonstrates an association between low urine output and adverse outcomes in pediatric patients[73] and adults,[52] urine output cannot be used to detect kidney damage. Changes of the SCr only become manifest after 50% of the renal mass is lost, leading to the decline of the GFR. Transient changes cannot be detected, although damage has occurred. Therefore, extensive work has identified new damage biomarkers that detect kidney damage before a functional decline (sCr increases and/or urinary output declines) occurs (Table 2).[74–76]

Recent studies have demonstrated that damage AKI biomarkers can detect kidney damage without loss of function.[74,75] Based on these studies, the term "subclinical AKI" was introduced (Figure 2).

Cardiopulmonary bypass, surgical trauma, or other noxious events might trigger the production and release of DAMPs, proinflammatory mediators, and possible biomarkers of early tubular stress. Different aspects of kidney function and different mechanisms of injury are reflected by different biomarkers. They are able to detect AKI earlier and might identify the underlying etiology. However, before implementing these biomarkers into daily practice, several issues have to be addressed, including the low sensitivity related to the etiological heterogeneity of AKI and low specificity related to extrarenal causes for fluctuations of biomarkers levels.[77] The performance of AKI biomarkers was very good when well-defined kidney injury was examined.[78] However, in heterogeneous patient populations with variable onset and causes of kidney injury, the performance of biomarkers was reduced. To increase the robustness of the predictive performance of AKI, the "renal angina" concept was introduced. This concept combines clinical conditions with comorbidities and biomarkers. Measurement of biomarkers in patients with a certain risk profile considerably improves the negative predictive value of the markers.[79]

Various interventions have been investigated to prevent the development of AKI, but only a few have achieved a promising result.

Hemodynamic Control

Autoregulatory mechanisms control renal blood flow within a broad range of pressures to maintain a stable GFR. Different factors and diseases, including hypertension, kidney disease, and major surgery, might disrupt renal autoregulation, leading to ischemia and kidney injury.[80] Reduced renal blood flow leads to renal hypoxia, inflammation, and fibrosis, which induce microvascular dysfunction in hemodynamic compromised conditions.[80,81] In acutely ill patients, renal ischemia is the most frequent and important pathogenetic AKI factor.[82] Prolonged episodes of hypotension in the intraoperative period may decrease renal perfusion, resulting in AKI in patients with impaired autoregulation.[83] A retrospective study including 5127 patients undergoing noncardiac surgery observed AKI when mean arterial pressure during surgery was <60 mm Hg for >20 minutes and <55 mm Hg for >10 minutes (adjusted OR, 2.34; 95% CI, 1.35–4.05).[84] Based on these data, the duration of a hypotensive episode should be kept as short as possible (Table 2).[84] A general recommendation for a sufficient mean arterial pressure is not available. However, a recently published trial suggests that individualized blood pressure control in the perioperative period might reduce the occurrence of AKI.[85] Optimizing the hemodynamic situation is required in patients at high risk for the development of AKI because it is well known that both hypotension and hypertension can negatively affect renal microcirculation in patients with compromised renal autoregulation.

Fluids

The main aim of volume resuscitation is the reestablishment of a stable hemodynamic situation and organ perfusion.[86] Several studies in critically ill patients demonstrated that volume overload is associated with organ edema, leading to the development of AKI and worsening of preexisting AKI.[58,87] Due to fluid overload and oliguria in critically ill patients with preexisting AKI, fluid management is very challenging. Hypovolemia and hypervolemia in critically ill patients increase morbidity as well as mortality. However, the intraoperative use of diuretics can only be recommended for managing severe fluid overload and not for preventing AKI.[2] In patients with preexisting renal dysfunction, an association between the use and dose of diuretics and the

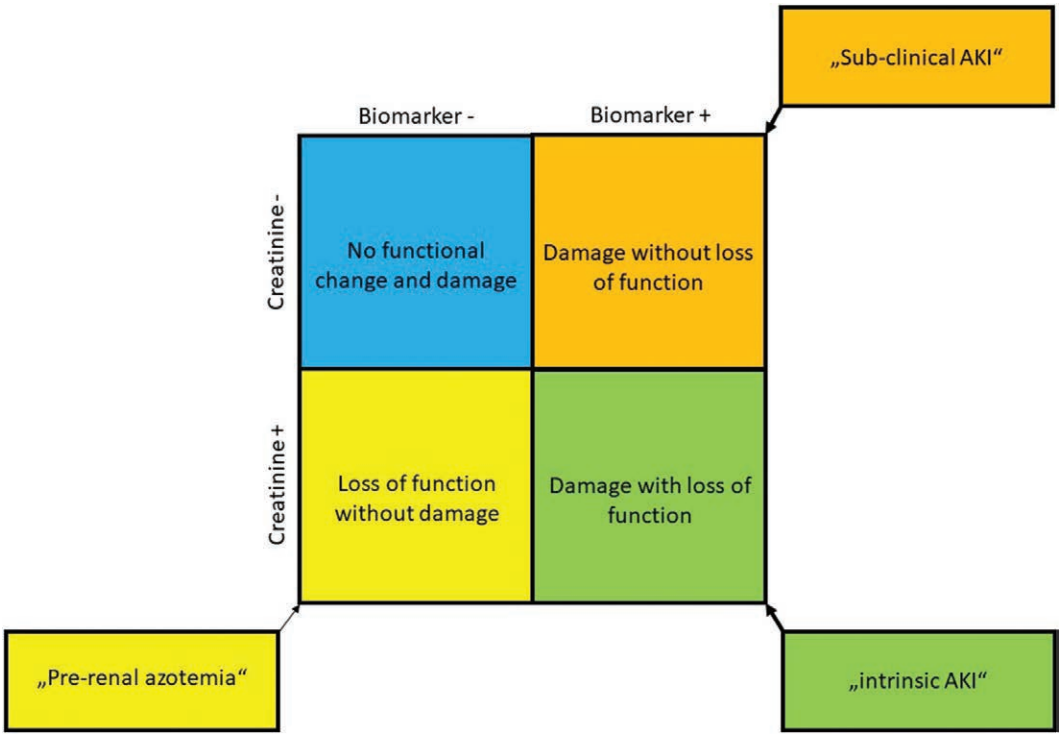

Figure 2. Subclinical AKI: damage without loss of function. Diagnosis of AKI based on damage markers (new biomarkers) and functional (SCr). The use of damage biomarkers allows a detection of kidney damage without a loss of function (subclinical AKI). AKI indicates acute kidney injury; SCr, serum creatinine.

development of AKI exists.[88] The amount and type of fluid together play a crucial role. Large amounts of 0.9% saline leads to hyperchloremic acidosis and renal vasoconstriction and increase the risk of AKI (Table 2).[89–91] Furthermore, the use of a saline-based solution strategy resulted in a higher postoperative incidence of AKI than the use of a chloride-restrictive fluid strategy.[92] Recently published trials demonstrated that the use of saline in critically ill patients resulted in a higher rate of the composite outcome from death from any cause, persistent renal dysfunction, or RRT than the use of balanced crystalloids.[48,93] Therefore, the use of balanced crystalloids and an adequate perioperative control ensuring hemodynamic stability are recommended.

Remote Ischemic Preconditioning

Remote ischemic preconditioning (RIPC) is a simple technique to provide organ protection. It is triggered by brief episodes of transient ischemia and reperfusion, and the protective effects are not limited to the organ or tissue receiving the preconditioning stimulus but were also traceable in remote organs.

Due to the kidney's high metabolic rate and complex vascular anatomy, it is particularly susceptible to ischemia reperfusion injury.[94] Thus, RIPC was speculated to be an effective procedure to trigger endogenous protection against renal ischemic damage. A typical method to induce RIPC is to put a blood pressure cuff around an arm and inflate the cuff up to 50 mm Hg above the systolic blood pressure to induce an ischemia. After a certain time point (normally 5 minutes), the cuff is deflated and reperfusion of the tissue is allowed. These cycles are repeated several times. To date, the underlying mechanisms of RIPC are not fully elucidated. Evidence indicates that RIPC leads to the release of DAMPs, which subsequently bind to pattern-recognition receptors on the surface of renal tubular epithelial cells, introducing a brief episode of cell cycle arrest through the release of alarm markers.[95]

Several clinical trials showed that RIPC can reduce the occurrence of AKI after surgery (Table 2),[96,97] whereas others showed no effect.[98,99] The results of the different trials are difficult to compare because of the use of different end points and the heterogeneity of trial designs and patient populations. However, it is important to note that some medications (eg, propofol, sulfonamide) mitigate the protective effects of RIPC. Although conflicting results exist, RIPC should be considered as a preventive measure because it does not impose additional costs, is easy to apply, and is not associated with complications.

KDIGO

The KDIGO guidelines propose to implement a bundle of preventive measures in patients at high risk for AKI. This bundle consists of maintenance of volume status and perfusion pressure, monitoring of SCr and urine output, discontinuation and avoidance of nephrotoxic agents, use of alternatives to radio contrast agents, maintenance of normoglycemia, and functional hemodynamic monitoring.[2] Recently, a single-center, randomized controlled clinical trial (PrevAKI) showed that biomarker-guided implementation of the KDIGO guidelines compared with standard care significantly decreased the occurrence of AKI in patients undergoing cardiac surgery (absolute risk reduction, 16.6%;

95 CI, 5.5–27.9; $P = .004$; Table 2).[100] In addition, another single-center trial investigating high-risk patients undergoing major abdominal surgery also demonstrated that optimizing the patients by using a prespecified bundle reduces the occurrence of moderate and severe AKI and shortens length of ICU and hospital stay.[101]

CONCLUSIONS

Overall, reducing exposure to nephrotoxins (including saline) can be advocated for all patients. After this, with respect to the heterogeneous nature of AKI, a complex multimodal treatment approach, including specific risk assessment, is advisable to prevent and manage AKI. Application of care bundles based on the KDIGO guideline appears to be effective in high-risk patients selected using AKI biomarkers.

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