Acute Kidney Injury in the Surgical Patient

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KEYWORDS

• Perioperative • Acute kidney injury • Chronic kidney disease • Complications

KEY POINTS

- Acute and chronic kidney injury and dysfunction play important roles in affecting perioperative outcomes.
- AKI is a common complication after surgery and mild to moderate AKI is more common than severe AKI.
- All stages of AKI severity are associated with increased short- and long-term morbidity and mortality.
- Clinical risk factors for AKI are similar but not identical in different surgical populations.

INTRODUCTION

Perioperative acute kidney injury (AKI), characterized by persistent oliguria or an increase in serum creatinine levels, is a common perioperative complication and is associated with up to a 10-fold increase in hospital cost and mortality, decreased long-term survival, and an increased risk for chronic kidney disease (CKD) and hemodialysis after discharge.[1–11] Depending on the type of surgical procedure that a patient undergoes, AKI complicates the perioperative hospital stay for up to 50% of surgical patients.[1,2,12–16] Nevertheless, AKI remains among the most underdiagnosed postoperative complications despite increasing understanding of its epidemiology and

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outcomes. Considering the high prevalence of AKI and the deleterious effect when it occurs, efforts must focus on AKI prevention, mitigation of further injury when AKI has already occurred, treatment of negative effects on other organs, and facilitation of renal recovery in patients with established AKI. Although the understanding of the mechanisms of AKI has grown substantially, and the emergence of new biomarkers and imaging techniques has provided new tools for early risk stratification and diagnosis, the translation of these discoveries into clinical practice has been slow. The well-defined timing of surgical physiologic stress on the kidney in the perioperative period provides a unique opportunity for early risk stratification to guide perioperative assessment and preventive therapies to achieve these goals.

DEFINITIONS, EPIDEMIOLOGY, AND OUTCOMES ASSOCIATED WITH PERIOPERATIVE ACUTE KIDNEY INJURY

Before 2004, the reported incidence of hospital-acquired AKI varied significantly from 1% to 31% due to the incoherent criteria used to define AKI and the focus placed on the most severe AKI defined either by a large increase in serum creatinine or by the need for renal replacement therapy (RRT).[17,18] In 2004, the Acute Dialysis Quality Initiative published Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE), a consensus definition for AKI, that for the first time included less severe AKI stages and provided a structured classification for severity and recovery.[19] The recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have expanded the AKI criteria to include changes as small as 0.3 mg/dL.[20] The reported epidemiology and outcomes of AKI have been under rapid evolution since the publication of these new definitions.

Surgical societies and registries have been slow in adopting these new definitions. The American College of Surgeons (ACS) Committee on Trauma defines acute renal failure as a serum creatinine increase greater than or equal to 3.5 mg/dL, but in a large multicenter trauma study, only 15% of all patients with AKI defined by RIFLE criteria had a peak creatinine value greater than 3 mg/dL.[2] The ACS National Surgical Quality Improvement Project (NSQIP) is the largest existing prospective surgical database that quantifies 30-day risk-adjusted surgical outcomes for patients undergoing major surgery, and it defines AKI as an increase in serum creatinine greater than 2 mg/dL from the patient's baseline or as the acute need for RRT.[21] Not surprisingly, studies using the ACS NSQIP database have demonstrated a substantial 30-day mortality associated with AKI and an incidence as low as 1%, creating the perception that postoperative AKI is a rare and often fatal complication after surgery.[22] In a recent single-center cohort study of greater than 20,000 postoperative patients, the ACS NSQIP definition for AKI severely underestimated the incidence of AKI defined by consensus criteria.[12]

The incidence of AKI in recent studies using the current consensus criteria ranges from 25% for trauma patients[2] to as high as 50% for patients undergoing aortic surgery or liver transplantation.[23,24] AKI has been demonstrated to be a common and serious postoperative complication associated with increased risk for short- and long-term mortality, increased incidence of CKD, increased incidence of other postoperative complications, and much higher resource utilization compared with patients with no postoperative AKI.[3,5,12,25–33] The risk-adjusted association between postoperative change in serum creatinine and adverse clinical outcomes is continuous and observed at even lower cutoffs than in the original RIFLE definition,[12,34] and it has been shown that the adverse effects of AKI, as defined by consensus criteria, persist for years even for those patients considered to have partial or even full recovery by the

time of hospital discharge.[3,4] The risk-adjusted average cost of care for these patients was $42,600 for patients with any AKI compared with $26,700 for patients without AKI.[1] Thus, prevention of postoperative AKI should be seen as an important target in standardized surgical practice and in studies focusing on quality measures that could translate into improved care for the surgical patient.

RISK FACTORS FOR ACUTE KIDNEY INJURY

Several preoperative and intraoperative factors have emerged as important and common predictors for AKI across different surgical populations (**Table 1**). Scoring systems have been used for years in an attempt to measure risk factors for adverse outcomes after surgery. Several existing scoring systems that measure the risk for AKI after cardiac surgery rely mostly on preoperative variables (reviewed in[35]). More novel preoperative factors such as total lymphocyte count less than 1500 cells/μL and elevated C-reactive protein were identified to be associated with AKI after cardiac surgery.[36,37] Genetic polymorphisms for selected inflammatory and vasoconstrictor genes (alleles angiotensinogen 842C and interleukin 6-572C in Caucasians, and endothelial nitric oxide synthase 894T and angiotensin-converting enzyme deletion and insertion in African Americans) provided 2-to 4-fold improvement over clinical factors alone in explaining postcardiac surgery AKI.[38] For patients undergoing noncardiac surgery, preoperative factors unique for the surgery type need to be considered.[39] Women undergoing surgery for any type of cancer, and especially those with metastatic cancer, had significantly higher odds of developing AKI.[14] Among patients undergoing orthotopic liver transplantation, the Model for End-Stage Liver Disease score, but not pretransplantation creatinine values, was predictive of AKI.[40] A low Norton scale score (a measure of a patient's risk for developing a pressure ulcer) and preoperative use of diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) were all associated with AKI following total hip arthroplasty.[41,42] Among patients undergoing endovascular abdominal aortic aneurysm repair, the use of fenestrated grafts and increasing contrast dose carried a higher risk for AKI.[43] In a large prospective study of severe trauma patients, any increase in serum creatinine on admission greater than that expected (based on a patients age, gender, and race), an increase in lactic acid, low body temperature, and any transfusion of packed red blood cells and cryoprecipitate within the first 24 hours of trauma were associated with the increased risk for subsequent AKI.[2] Attempting to create a meaningful risk calculation for AKI from these disparate factors has been challenging.

Although some of these factors are unavoidable, others are both preventable and largely ignored in routine clinical practice. Preoperative assessment of kidney health using readily available clinical tests—urinary albuminuria and estimated glomerular filtration rate (eGFR) using serum creatinine—is one of the least used yet most valuable clinical resources not only for the assessment of the risk for AKI but also for the overall risk for postoperative morbidity and mortality. CKD affects 5% of the US population[44] and is an independent predictor of mortality and cardiovascular events.[45] A systematic review of 31 cohort studies of patients undergoing elective surgery demonstrated a graded relationship between CKD severity and postoperative death, comparable to that seen with diabetes, stroke, and coronary disease.[46] In a recent analysis of the ACS NSQIP database, the adjusted hazard ratio for 30-day mortality ranged from 2.30 for stage 3 CKD to 3.05 for stage 5 CKD compared with no CKD.[47] Furthermore, preoperative proteinuria, independent of preoperative eGFR and other comorbidities, was not only associated with the risk of AKI but also a powerful independent risk factor for long-term all-cause mortality and end-stage

Table 1
Risk factors for acute kidney injury

Type of Surgery	Preoperative Risk Factors	Intraoperative Risk Factors
Cardiac surgery	Advanced age Female sex Baseline renal function Diabetes mellitus Poor glycemic control Congestive heart failure Low ejection fraction Peripheral vascular disease Intra-aortic balloon pump use Chronic obstructive pulmonary disease Peripheral vascular disease Hypertension Lower preoperative hemoglobin Atrial fibrillation Preoperative total lymphocyte count <1500 cells/μL Gene polymorphisms (Alleles angiotensinogen 842C and interleukin 6-572C in Caucasians; alleles endothelial nitric oxide synthase 894T and angiotensin-converting enzyme deletion and insertion in African Americans) Elevated preoperative C-reactive protein	Emergent reoperation Valve replacement surgery Surgery on the thoracic aorta Deep hypothermic circulatory arrest Low-output syndrome Vasopressors needed before cardiopulmonary bypass Use of cardiopulmonary bypass Volume of blood transfusion Intraoperative nadir hemoglobin level Intraoperative hypotension (<50 mm Hg) Urine output Surgery requiring cardiopulmonary bypass Cardiopulmonary bypass duration Low pump flow Low perfusion pressure Severe hemodilution Low oxygen delivery (DO_2) and low DO_2/VCO_2 ratios Hyperthermia (the arterial outlet temperature >37°C) Intraoperative inotropes Furosemide administration ICU admission temperature after CPB Aprotinin use
Noncardiac surgery	Advanced age Male sex Baseline renal function Diabetes mellitus Liver disease Peripheral vascular disease Chronic obstructive pulmonary disease Left ventricular dysfunction High body mass index American Society of Anesthesiologists physical status Preoperative albumin <3.2 Preoperative anemia Use of hydroxyethyl starch fluids Model for end-stage liver disease score, hepatorenal syndrome type II, and hepatitis C (orthotopic liver transplantation) Low Norton scores (performed by nurses) and preoperative diuretics and NSAIDS (total hip arthroplasty)	Emergent surgery High-risk surgery Reoperation Open vascular surgery procedure Surgery for malignant gynecologic tumors Prolonged surgical times (>4 h) Aortic cross-clamp time Fenestrated grafts and contrast dose for endovascular procedures Intraoperative hypotension Intraoperative vasopressor use Number of transfused packed red blood cells Prolonged dopamine use Lactic acidosis Lateral decubitus positioning in laparoscopic surgery Administration of furosemide or mannitol Duration of anhepatic phase (orthotopic liver transplantation)

renal disease after cardiac surgery.[48,49] However, the importance of CKD as a perioperative risk factor is still not widely appreciated among physicians involved in perioperative decision-making.

Some perioperative risk indicators consider CKD an important prognostic factor in postoperative risk assessment,[50–52] whereas others do not.[53,54] One difficulty in increasing the awareness of CKD as an important perioperative risk factor is the complicated relationship between serum creatinine and eGFR calculated with commonly used estimation equations such as the Chronic Kidney Disease Epidemiology Collaboration equation.[55] Especially among women and the elderly, the serum creatinine alone may not give an accurate picture of CKD because creatinine values within normal limits may correspond to a low eGFR. Thus, in the perioperative setting, use of estimation equations to assess eGFR, rather than relying on serum creatinine values alone, is a strategy to assure that CKD is appropriately assessed as a risk factor for not only AKI but also overall postoperative mortality.

One factor that has received intense interest recently has been the possible effect of preoperative medications on preoperative complications. Statins (or HMG-CoA reductase inhibitors) have received the most attention because of their important pleiotropic effects, including reduced vascular inflammation and improved endothelial function.[56] The data on preoperative statin use and risk for AKI are evolving and contradictory. The subgroup analysis of a systematic review of preoperative use of statins among cardiac surgery patients (including 4 studies with a total of 367 patients, including 19 patients with renal failure) demonstrated no benefit from preoperative statin use.[57] A study from The Cleveland Clinic reporting no difference in AKI or hospital mortality between 4683 statin users propensity matched with 22,000 nonstatin users was limited to elective surgery cases and reported a very low incidence of AKI (6%), hospital mortality (0.6%), and need for dialysis (0.05%), rendering it difficult to compare to other studies. In a small cohort of 151 vascular surgery patients, Kor and colleagues[58] found no difference with preoperative statin use using moderate to severe AKI (incidence 7%), need for RRT (3%), and mortality (5%) as endpoints.[57] In contrast, a population-based Canadian retrospective cohort study including 213,347 older patients who underwent major elective surgery demonstrated 16% lower odds of severe AKI, 17% lower odds of acute dialysis, and 21% lower odds of mortality for patients on a preoperative statin.[59] In a retrospective cohort of 98,939 patients undergoing a major open abdominal, cardiac, thoracic, or vascular procedure, preoperative statin use was associated with a 20% to 26% reduction in the incidence of postoperative AKI defined by consensus criteria.[60] These retrospective results, and the intriguing pleiotropic actions of statins, have prompted several prospective trials on the effect of statins on perioperative complications.

Several modifiable intraoperative factors have been identified as risk factors for AKI for both cardiac and noncardiac surgery, including use of cardiopulmonary bypass (CPB), hemodilution, intraoperative transfusion and hemoglobin levels, hypotension, oxygen delivery and any use of diuretics, vasopressors, and inotropes.[61–64] Rewarming after CPB and hyperthermic perfusion during CPB are novel risk factors for AKI after cardiac surgery.[65,66] A recent systematic review of perioperative interventions aimed to optimize global blood flow showed no difference in mortality, but the rates of renal failure (relative risk 0.71, 95% confidence interval [CI] 0.57–0.90) were reduced.[67] Goal-directed intraoperative management to reduce the risk of postoperative AKI through optimizing renal perfusion is both feasible and underused.

RISK STRATIFICATION FOR ACUTE KIDNEY INJURY

Given that AKI is common after surgery, and associated with significant morbidity and cost, the ability to detect AKI within hours of onset would likely be helpful in implementing measures to protect the kidney from further injury and to preserve renal function. In the presence of common clinical risk factors for perioperative AKI, such as hypotension or hypoxemia or certain comorbidities, it is difficult to discriminate those who will imminently develop AKI from those who will not before change in creatinine or urine output is measurable. Widespread adoption of effective preventive interventions is only likely with the assistance of a test or tests that can be quickly done at the bedside and that reliably discern those patients at increased risk for AKI from those at low risk.

Use of Imaging Techniques

Ultrasound and Doppler imaging of the kidney have been used for years in the assessment of CKD in the transplanted kidney and in renal artery stenosis. Doppler imaging detects macroscopic vascular abnormalities as well as microvascular changes in blood flow in the kidney. Renal resistive index (RRI), determined by Doppler ultrasonography, quantifies changes in renal vascular resistance, and recent studies have shown that an elevated RRI is associated with an increased risk for AKI.[68] In patients with septic shock, an increased RRI has been shown to be associated with AKI.[69–71] The RRI, when used in the immediate postoperative period after cardiac surgery with cardiopulmonary bypass, predicts delayed AKI and its severity.[72] When measured using intraoperative transesophageal echocardiography, for patients undergoing cardiac surgery, the predictive results for AKI are comparable to RRI obtained via translumbar ultrasound.[73] The association between elevated RRI and AKI holds for noncardiac surgeries like orthopedic surgeries and in critically ill patients in the medical intensive care unit (ICU).[74,75] RRI has also been shown to be helpful in predicting the progression of postoperative AKI after cardiac surgery.[76] Although RRI is closely related to renal vascular resistance, it has become clear in recent studies that there are other factors that affect RRI especially in the unstable patient, and the indications and utility of the test for predicting AKI are still unresolved.[77,78] Another newly developed technique for assessing renal microvasculature is contrast-enhanced ultrasonography (CEUS) to assess renal perfusion.[79] A recent study of patients undergoing elective cardiac surgery, who were considered to be at risk of AKI and were studied with CEUS, showed that renal perfusion decreased within 24 hours after surgery. The technique of CEUS has been validated in the quantification of microcirculatory flow in the liver and the heart and shows early promise in assessing the risk of AKI.[80]

MRI is another emerging modality in the early diagnosis of AKI. Newer and less toxic contrast agents, including ultrasmall particles of iron oxide, are being studied for imaging renal blood flow and volume.[81] Blood oxygenation level dependent (BOLD) MRI, which uses deoxyhemoglobin as an endogenous contrast agent for the noninvasive assessment of tissue oxygen bioavailability, has been used to evaluate intrarenal oxygenation.[82] Changes in medullary blood flow related to the use of nephrotoxic agents, including NSAIDs, intravenous contrast agents, and calcineurin inhibitors, are effectively demonstrated with BOLD MRI.[83] It has recently been used to study changes in medullary blood flow associated with hypertension and CKD.[84–86] BOLD MRI has been used to study renal oxygenation and function in animal models of AKI[87,88]; however, one recent study using BOLD MRI in patients with AKI found no correlation between MRI findings and GFR.[89] As with the Doppler ultrasound-derived

RRI, the indications and utility of BOLD MRI for predicting AKI in surgical patients are still unresolved.

Use of Urine and Plasma Biomarkers

Another approach for rapid diagnosis of organ injury is the analysis of serum or urine biomarkers that reveal early evidence of cellular stress or injury. Biomarkers for cardiac injury, such as serum troponin, are useful in the evaluation and treatment of patients with chest pain because they help clinicians identify those patients who have undergone recent myocardial injury. Many serum and urine biomarkers have been studied for their ability to predict AKI (reviewed in[90–94]). Difficulties in finding biomarkers with good predictive power include the variable time from insult to the development of AKI, the association of biomarkers with both CKD and AKI, and their association with the diverse underlying disease processes that can cause AKI. Furthermore, surgical and critically ill patients are exposed to systemic inflammation with cellular stress and injuries in several organs, repetitive exposure to invasive procedures and hemodynamic perturbations requiring fluid therapy and vasopressor support, blood transfusion, and nephrotoxic drugs. The abundance of these potential mediators and confounders of AKI may cause nonspecific increases in biomarkers reflecting overall illness severity rather than specific organ damage.

Among surgical patients, the use of biomarkers for AKI prediction was most studied after cardiac procedures with the most promising results demonstrated for the use of plasma and urine neutrophil gelatinase-associated lipocalin (NGAL) (reviewed in[94,95]). Systemic inflammation induces NGAL synthesis by extrarenal tissues and the release of NGAL from neutrophils mainly in the dimeric form. A recent systematic review summarized studies that measured NGAL in more than 7000 patients after cardiac surgery and showed moderate overall discriminatory ability with area under the receiver operating characteristic curve (ROC-AUC) between 0.82 and 0.83. Studies including more than 8500 critically ill patients, mostly recruited from mixed medical/surgical ICU populations, demonstrated similar overall predictive performance with ROC-AUC between 0.79 and 0.80.[96,97] The inability to distinguish systemic inflammatory effects from organ-specific increases in NGAL, and the lack of a diagnostic platform to differentiate specific biological forms of NGAL, has hampered widespread clinical use of this biomarker.

Cystatin C (CyC) is the most studied novel functional kidney biomarker.[92] This cysteine protease inhibitor is produced by all nucleated cells of the body, released into the bloodstream at a constant rate, excreted through glomerular filtration into primary urine, and subsequently completely reabsorbed and catabolized in proximal renal tubules. As a consequence, CyC is not normally found in urine in significant amounts, and urinary CyC may reflect tubular damage. Because of the constant rate of its production, plasma CyC concentrations may be a better marker of GFR than creatinine in surgical patients. However, its ability to provide early risk stratification for postoperative AKI or RRT requirement remains uncertain among surgical patients.[92]

Recently, 2 urinary biomarkers, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), have been validated as markers of risk for AKI.[98,99] These markers were recently approved for use by the US Food and Drug Administration, becoming the first AKI biomarkers to do so. A multicenter study involving 420 patients found that urinary [TIMP-2]•[IGFBP7] was predictive of moderate to severe AKI in critically ill patients within 12 hours. Unlike prior studies evaluating these markers or others for AKI,[98] the endpoint was adjudicated by a committee of 3 independent experts who were blinded to the results of the

test. The ROC-AUC for the urinary [TIMP-2]•[IGFBP7] test was 0.82 (95% CI 0.76–0.88) and was superior to simultaneously measured serum creatinine and other existing biomarkers for predicting the risk of imminent AKI. Patients with a urinary test result higher than the prespecified high sensitivity cutoff value of 0.3 $(ng/mL)^2/1000$ had 7 times the risk for AKI (95% CI 4–22). Meersch and colleagues[100] examined the sensitivity and specificity of the [TIMP-2]•[IGFBP7] test for any AKI stage among patients undergoing cardiac surgery and found a sensitivity of 0.92 and specificity of 0.81 for a cutoff value of 0.5 (ROC-AUC of 0.84) using the highest urinary [TIMP-2]•[IGFBP7] achieved in the first 24 hours following surgery. Interestingly, TIMP-2 and IGFBP7 are both associated with G1 cell-cycle arrest, an epithelial cellular protective mechanism, rather than with cellular necrosis or apoptosis. Epithelial cells, by virtue of their anatomy and function, are susceptible to multiple environmental stressors: toxin exposure, oxidative stress, and inflammation among others. When DNA may be damaged, or when bioenergetic resources are scarce, epithelial cells may enter cell-cycle arrest to protect themselves, and TIMP-2 and IGFBP7 become elevated. Thus, these urinary biomarkers may indicate risk for injury before any actual AKI takes place.

Use of Clinical Prediction Scores

One very different approach toward early diagnosis and prediction of organ injury is automated analysis of the large amounts of clinical data obtained during routine care to detect critical incidents or trends that might be predictive of injury. Accurate risk stratification of patients in real time could enable the selection of optimal therapy in a timely fashion to prevent AKI altogether, or to mitigate the effects of the complication even before signs and symptoms arise, and could be tailored to a patient's personal clinical profile. Despite the acquisition of multiple continuously recorded physiologic signals during modern perioperative management, the use of these data for the development of risk and prediction models has been limited to the prediction of broad outcomes such as postoperative mortality rather than to specific morbidity events including AKI.[101–103] Most of the predictive scores and algorithms have been limited either to a specific type of surgery or to preoperative risk factors only, or have used the occurrence of the most severe AKI as an endpoint while excluding the more prevalent mild and moderate AKI.

Most of the studies that developed and validated predictive models or clinical scores for AKI were performed among cardiac surgery patients. A recent systematic review[35] evaluated the available risk models for AKI after cardiac surgery and reported 4 clinical risk scores for AKI requiring dialysis,[104–107] and 3 scores to predict a broader definition of AKI.[108–110] These scores predicted a probability of severe AKI between less than 1% and greater than 20%, with the ROC-AUC varying between 0.77 and 0.84. For patients undergoing noncardiac surgery, a few predictive models, developed in small cohorts using limited intraoperative data or in larger cohorts but using only severe AKI as an endpoint, are further limited by the lack of validation studies and provide only modest predictive accuracy.[22,111–113] Recently, the UK AKI in Cardiac Surgery Collaborators group have developed and validated a new risk prediction score for any stage AKI after cardiac surgery with ROC-AUC of 0.74, providing better discrimination compared with previously published scores.[114]

The volume of physiologic data routinely acquired during intraoperative hemodynamic monitoring is rarely used in published risk scores and, when used, it is usually summarized by some reductionist approach (mean, lowest value) rather than applied in their continuity and complexity and almost never in automatized fashion.[13,22,105,111,112,115–120] Lack of sophistication in both data collection and

analysis of real-time physiologic data has limited this approach. Automated risk scores, developed using machine learning to automatically analyze physiologic time series data, have already been shown to predict neonatal clinical outcomes more accurately than can be achieved with any pre-existing scoring system.[121] Machine learning applied to the automated, rapid, noninvasive measurements obtained in the operating room and ICU raises the prospect of real-time risk prediction for perioperative AKI and studies using them are starting to emerge.[34,122–124]

PREVENTION AND TREATMENT OF PERIOPERATIVE ACUTE KIDNEY INJURY

One of the challenges in managing AKI is the paucity of interventions to treat it once it occurs. Given that reality, prevention of AKI is of paramount importance. Many interventions have been studied in an attempt to prevent or ameliorate perioperative AKI.[13,15,16] Although patients with CKD have a higher risk for adverse perioperative events, preoperative optimization of renal function using pharmacologic therapy, such as angiotensin converting enzyme inhibitors (ACE-I), diuretic therapy, or regular visits to a nephrologist, to prevent a decline in kidney function around the time of surgery was not proven to mitigate the risk of AKI.[112,125] Some investigators advocate avoidance of ACE-I or angiotensin receptor blocker therapies around the time of surgery, especially when hypotension is anticipated.[125,126] Multiple pharmacologic therapies have been unsuccessfully tested for the prevention of perioperative AKI, including scavengers of oxygen free radicals such as mannitol and N-acetylcysteine, dopamine, fenoldapam, loop diuretics, and atrial natriuretic peptide (reviewed in[13,15,16,127]). A recent systematic review and meta-analysis including 1079 patients in 5 randomized control trials demonstrated no benefit for the prophylactic perioperative use of sodium bicarbonate for prevention of AKI after cardiac surgery. In contrast, the use of sodium bicarbonate prolonged the duration of mechanical ventilation and ICU length of stay and increased the risk of alkalemia.[128] A recent large randomized clinical trial of patients undergoing noncardiac surgery found that neither aspirin nor clonidine administered perioperatively reduced the risk of AKI (13.4% for aspirin vs 12.3% for placebo; 13.0% for clonidine vs 12.7% for placebo), whereas both aspirin and clonidine were associated with clinically important adverse effects.[129]

Some aspects of perioperative management do appear to have an important effect on kidney function. The use of off-pump technique in cardiac surgery has demonstrated benefit in randomized control trials and meta-analyses.[115] Two large meta-analyses and a systematic review have showed that intraoperative interventions associated with goal-directed fluid management were associated with a significant reduction in the incidence of all severity stages of AKI.[67,130] Initiating appropriate hemodynamic monitoring to allow the anesthesiologist to optimize intravascular volume, cardiac output, or oxygen delivery in high-risk patients resulted in a decreased risk of perioperative AKI if started preoperatively (odds ratio 0.70, 95% CI 0.53–0.94; $P = .02$) or intraoperatively (OR 0.47, 95% CI 0.27–0.81; $P = .006$).[130] One contentious and unresolved issue in goal-directed fluid management and resuscitation is the optimal endpoint and how to measure it. An optimal mean arterial pressure (MAP) for the kidney at risk for AKI is unknown and may be different from that obtained peripherally.[80] The ability to assess renal perfusion at the bedside using Doppler ultrasound may provide better fluid and vasoactive medication management for the unstable patient at risk for AKI. One study in patients with septic shock showed that RRI decreased significantly when MAP was increased using norepinephrine from 65 to 75 mm Hg.[69] Another prospective study of patients who had experienced sustained

hypotension showed that an average MAP between 72 and 82 mm Hg during the first 3 days after hypotension was associated with a lower incidence of RIFLE-AKI compared with patients with an average MAP less than 72 mm Hg.[131] Further studies exploring the optimal resuscitation endpoints for the kidney to prevent AKI, and how to measure those endpoints, are needed. Another interesting meta-analysis involving 1600 patients in 10 trials demonstrated that volatile anesthetics may provide renal protection in patients undergoing cardiac surgery and supports the notion that further research of high methodologic quality is needed to define optimal intraoperative management of patients at high risk of AKI.[132]

Another evolving concept is the use of remote ischemic preconditioning to prevent AKI in certain patient populations. Ischemia reperfusion injury occurs whenever a tissue bed becomes temporarily ischemic and is then restored to normal perfusion. The kidneys are particularly sensitive to ischemia reperfusion injury due to their high metabolic and oxygen demands and complex microvasculature.[68] However, in addition to causing injury, programmed brief and intermittent ischemia is known to have cytoprotective effects. Local ischemic preconditioning has been shown to be effective against various types of AKI.[133,134] Remote ischemic preconditioning, involving programmed brief and repeated ischemia of a remote tissue such as limb skeletal muscle, has been shown to be as effective as local ischemic preconditioning in preventing cellular damage. It is thought to attenuate injury through upregulation of a variety of intracellular kinases, resulting in modification of mitochondrial function, metabolic downregulation, and temporary cell-cycle arrest.[135] Recently, in a randomized controlled trial, remote ischemic preconditioning was found to be protective against contrast medium–induced AKI for patients undergoing elective coronary angiography and who were judged to be at high risk for AKI.[133] Similar results were found in a randomized controlled trial of 120 patients undergoing elective cardiac surgery, in which the patients randomized to remote ischemic preconditioning had significantly less risk of postoperative AKI.[129] Although these early trials provide the promise of a novel, noninvasive, and virtually morbidity-free therapy to prevent AKI, further investigation is needed to define the indications and utility of this approach.

One important potential method of limiting the consequences of AKI in surgical patients is early and continued involvement of a nephrologist. A study from 2 hospitals in the United Kingdom with no on-site nephrology services showed that, compared with hospitals with nephrology consultation available, there were significant shortcomings in AKI recognition and management that were associated with poor survival and increased rates of CKD.[136] In prospective observational studies of the patient admitted to the ICU, it has been shown that delayed nephrology consultation was associated with higher mortality[137,138] and increased dialysis-dependence rates at hospital discharge.[138] In a recent prospective controlled nonrandomized study, patients in an early nephrology consultation group (seen within 18 hours of onset of AKI) had significantly lower risk of further decrease in kidney function.[139]

Nephrology referral has also been shown to be important in follow-up care after an episode of AKI. A study of patients who sustained AKI between 2003 and 2008 in a Veterans Administration hospital, and were considered to be at risk for subsequent worsening of renal function, showed that the cumulative incidence of outpatient nephrology referrals for these patients was only 8.5%.[140] Another more recent study of Veterans Administration patients admitted to the hospital with AKI showed that measurement of serum creatinine during outpatient follow-up was common, but measurement of proteinuria, parathyroid hormone, or serum phosphorus was rare.[141] The importance of this low referral rate is emphasized in a cohort study of hospitalized adults with AKI who received temporary inpatient dialysis and survived for 90 days

following discharge, in which patients with early nephrology follow-up had significantly lower all-cause mortality.[142]

Given the association between AKI and the later development of CKD and other complications, follow-up care for patients who sustain AKI in the hospital could have important public health and socioeconomic impact.[143,144] In 2012, the KDIGO AKI work group released guidelines recommending that patients be evaluated 3 months after AKI for the new onset of CKD or worsening of any pre-existing CKD.[145] Patients with CKD are to be managed according to the Kidney Disease Outcome Quality Initiative (KDOQI) CKD guidelines, and patients with no CKD are to be managed according to the KDOQI guidelines for patients at risk for CKD. Finally, in addition to nephrology consultation for the patient who has sustained AKI, it is imperative that primary care practitioners understand the risks associated with even mild degrees of AKI suffered by their patients, both to initiate timely nephrology involvement and to optimally manage patients at risk for the development of CKD.[146–148] The current attempts at better coordinating care for the patient with chronic disease, including the patient-centered medical home and accountable-care organizations with robust electronic medical record-keeping, may help improve the care of patients who have sustained AKI.[149–151]

SUMMARY

Acute and chronic kidney injury and dysfunction play important roles in affecting perioperative outcomes. AKI is a common complication after surgery and mild to moderate AKI is more common than severe AKI. All stages of AKI severity are associated with increased short- and long-term morbidity and mortality. Clinical risk factors for AKI are similar but not identical in different surgical populations. There seems to be no single therapy that will prevent perioperative AKI. Considering the high prevalence of AKI and the deleterious effect when it occurs, effort must focus on prevention of AKI, mitigation of further injury when AKI has already occurred, treatment of negative effects on other organs, and facilitation of renal recovery in patients with established AKI. This clinical pathway requires a medical team of experts, including all primary health care providers who manage surgical and critically ill patients, backed up by bedside nurses, pharmacists, and nephrologists. Every patient admitted needs a comprehensive and systematic assessment of kidney health. Current strategies should focus on better management of the preoperative risks and susceptibilities for AKI by more accurate assessment of the patient's renal reserve and susceptibility to new injury. A standardized approach for intraoperative management for patients at high risk for AKI needs to focus on avoidance of hemodynamic derangements that have been shown to impact renal function. In the early postoperative period, the magnitude of exposures to insult and the extent of the sustained renal distress or damage need to be evaluated using a combination of clinical parameters, novel biomarkers, and evolving imaging techniques. The determination of potential causes of AKI, the initiation of treatment, and then continued reassessment in response to that therapy should follow promptly afterward with the early involvement of nephrology teams.

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