Perioperative Acute Kidney Injury: Diagnosis, Prediction, Prevention, and Treatment

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Acute kidney injury (AKI) after surgery has been consistently associated with long-term morbidity,[1] mortality,[2] and healthcare costs.[3] Furthermore, the relationship persists even among patients with complete renal recovery,[4] or patients with minor perturbations in renal function not reaching the threshold for AKI.[5] The mechanism, pathogenesis, and risk factors for postoperative AKI vary significantly by surgical type and corresponding perioperative stressors.

Because treatment options for postoperative AKI are limited,[6,7] perioperative management has traditionally focused on prevention and diagnosis. Identifying prerenal (hypoperfusion), postrenal (outflow obstruction), and intrinsic renal (ischemic or nephrotoxic injury) causes are crucial first steps in the management of AKI.[7] Additionally, the 2012 Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guidelines emphasize severity-based management of AKI.[8] In patients with normal kidney function and mild AKI, management focuses on rapid identification and avoidance of nephrotoxic insults plus attention to volume status and renal perfusion pressure.[7] As the severity of AKI increases, the accompanying disruption to acid–base status and electrolyte balance may necessitate focused medical and supportive therapies, with renal replacement therapy and/or intensive care admission for the most severe cases.[7]

In this review, we define AKI in the perioperative setting, describe the epidemiologic burden, discuss procedure-specific risk factors, detail principles of management, and highlight areas of ongoing controversy and research.

Diagnostic Criteria

Common definitions of AKI rely on changes in serum creatinine and absolute urine output to provide an easy to interpret, objective, and validated approach useful for epidemiologic studies; however, each component of common AKI metrics has limitations.[8] Notably, urine output is significantly influenced by hypovolemia and diuretics, decreasing specificity, while serum creatinine only begins to increase after 50% of functional nephrons are lost, and these changes may not manifest for 48 to 72 h after injury, leading to low sensitivity in previously healthy kidneys.[7] Furthermore, serum creatinine can be impacted by nonrenal factors including age, muscle mass, nutritional status, liver function, and gastrointestinal elimination, further limiting diagnostic accuracy,[9,10] and not all patients have a recorded baseline serum creatinine. Despite these limitations, serum creatinine remains the standard biomarker for AKI in perioperative practice.[10]

The KDIGO criteria, currently used to define AKI,[8] update two previous consensus definitions, (1) Risk, Injury, Failure, Loss, End-stage Renal Disease (RIFLE)[11] and (2) AKI-Network (AKIN),[12] to capture patients with smaller creatinine increases, allowing earlier disease detection.[13]

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KDIGO AKI Consensus Definition

Currently, the perioperative medical community has largely adopted the KDIGO consensus criteria to define postoperative AKI within 7 days of an operative intervention. The KDIGO consensus criteria, published in 2012, included a few modifications from previous consensus definitions. Notably, the surveillance window for the relative changes in serum creatinine was extended to 7 days (the time window for the absolute increase of 0.3 mg/dl or greater rise in serum creatinine remains at 48 h). Additionally, the requirement for stage 3 AKI that serum creatinine increase by 0.5 mg/dl or greater in those with serum creatinine 4.0 mg/dl or greater was removed, and estimated glomerular filtration rate–based criteria for pediatric patients were added (table 1).[8]

Nomenclature as a Function of Chronicity

When KDIGO AKI (stage 1 or greater) persists for more than 7 days after the inciting event, it is termed acute kidney disease.[14] When the disease process persists beyond 90 days, it transitions from acute kidney disease to chronic kidney disease.

Pathophysiology

AKI represents a clinical syndrome, rather than a single disease, with most cases being multifactorial. Commonly implicated mechanisms include (1) oxido-inflammatory stress (for example, hyperoxia or glyco-oxidative injury), (2) renal hypoperfusion (for example, hypotension or anemia), (3) endogenous or exogenous nephrotoxins, and (4) iatrogenic causes (fig. 1). Venous congestion has also been associated with postoperative AKI through multiple potential mechanisms including (1) hypoperfusion, (2) inflammation, (3) oxidative stress, (4) endothelial activation, and (5) sympathetic activation.[15] Administration of nephrotoxic drugs and the need for intravenous contrast also place surgical patients at risk for acute interstitial nephritis and acute tubular damage.[16] Prerenal etiologies, like true volume depletion and volume dysregulation secondary to congestive heart failure, and acute tubular injury from a myriad of insults including nephrotoxic drugs and intravenous contrast, are common mechanisms in the postoperative setting. The surgical environment also introduces the possibility of iatrogenic injury. Examples include ureteral damage in an intraabdominal surgery and emboli from vascular procedures.

Incidence and Epidemiology

The incidence of AKI varies with socioeconomic status, healthcare setting, and population risk profile.[17] AKI in the surgical population is usually reported separately for (1) cardiac surgery and (2) noncardiac surgery populations. The pooled incidence of any stage of cardiac surgery–associated AKI in a meta-analysis of 320,086 cardiac surgery patients worldwide was 22.3% (95% CI, 19.8 to 25.1).[18] Of the patients, 13.6% were classified as stage 1, 3.8% were stage 2, 2.7% were stage 3 (without renal replacement therapy), and 2.3% were stage 3 (requiring renal replacement therapy).[18]

AKI is also a frequent complication after thoracic surgery. The incidence varies significantly based upon the extent of the procedure: (1) sublobar resection, 3.8% (2.0 to 6.2%); (2) lobectomy, 6.7% (4.1 to 9.9%); (3) bilobectomy or pneumonectomy, 12.1% (8.1 to 16.6%); and (4) esophagectomy, 10.5% (5.6 to 16.7%).[19] Risk factors for AKI after thoracic surgery are advanced age, male sex, higher body mass index, higher American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status classification, hypertension, diabetes, long-term angiotensin-converting enzyme inhibitor or angiotensin receptor blockers use, hypoalbuminemia, lower pulmonary function, extent or duration of surgery, intraoperative colloid administration, and higher estimated blood loss.[19]

The incidence of AKI after noncardiac or nonthoracic surgery varies substantially based upon the type of procedure. Data from 37,345 noncardiac surgeries demonstrated a total AKI incidence of 4.7% (KDIGO stage 1, 2.9%; stage 2, 0.7%; and stage 3, 1.1%).[5] A smaller, retrospective study of 1,869 noncardiac surgical procedures found 128 (6.8%) cases of AKI, divided between 5.4% KDIGO stage 1 and 1.4% KDIGO stage 2 or 3.[1]

Patients undergoing major vascular surgery have also been shown to have an increased risk for postoperative

Table 1. KDIGO Diagnostic Criteria

Stage	1	2	3
Serum creatinine	• Increased 1.5–1.9 times within 7 days or increased ≥ 0.3 mg/dl (26.5 μmol/l) within 48 h	• Serum creatinine: increased 2–2.9 times within 7 days	• Serum creatinine: increased > 3 times or ≥ 4 mg/dl (353.6 μmol/l) • Estimated glomerular filtration rate to < 35 ml·min^{-1}·1.73 m^{-2} in patients < 18 yr old • Initiation of renal replacement therapy
Urine output	• < 0.5 ml · kg^{-1}· h^{-1} for 6–12 h	• < 0.5 ml · kg^{-1} · h^{-1} for ≥ 12 h	• < 0.3 ml · kg^{-1} · h^{-1} for > 24 h or anuria for ≥ 12 h

KDIGO, Kidney Disease: Improving Global Outcomes.
Khwaja A: KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120:c179–84.

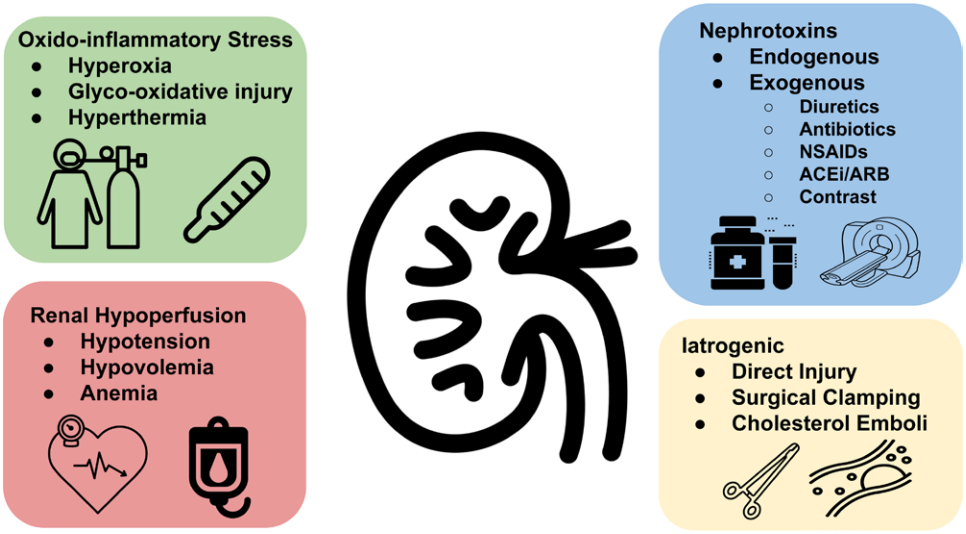

Fig. 1. Pathophysiology of perioperative acute kidney injury. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, Nonsteroidal anti-inflammatory drug.

AKI due to a combination of patient and surgical risk factors. Although the incidence across all vascular procedures is estimated to be as high as 49%,[3] the incidence differs dramatically based on specific procedure. For example, procedures on the lower extremities have a relatively low incidence of AKI (4% for infrainguinal bypass; 19% for endovascular revascularization of critical limb ischemia).[3] This contrasts with much higher incidence in aneurysm repairs, with some reports as high as 75% for emergent, open repair of a ruptured aneurysm.[20]

Retrospective studies place the incidence in noncardiothoracic, nonvascular surgery between 6 and 13%, depending on the diagnostic criteria used.[21–23] Trauma patients are at increased risk for AKI due to a variety of overlapping mechanisms, including renal hypoperfusion (due to hemorrhagic shock), direct renal injury, rhabdomyolysis, abdominal compartment syndrome, and nephrotoxic exposure.[24] Independent risk factors for the development of AKI after trauma include (1) older age, (2) blood transfusion, (3) comorbidities like diabetes or chronic kidney disease, (4) systolic blood pressure upon admission, and (5) lactic acidosis.[24] The incidence of AKI in the trauma population ranges from 12% in the general population to 20% in the population admitted to the intensive care unit (ICU).[25]

The incidence of AKI varies dramatically within intraabdominal surgery from 0.2% after appendectomy to 3.5% in exploratory laparotomies.[26] The overall incidence is 1.1%. More than half of liver transplant recipients experience postoperative AKI,[27] with a recent study demonstrating a significant proportion of stage 2 (24.9%) or stage 3 (17.7%) AKI.[28]

Risk Factors

Risk factors for postoperative AKI can generally be divided as (1) patient-related, (2) surgery-related, (3) anesthetic-related, and (4) postoperative risk factors.[2]

Validated Risk Models

Although many predictive models have been published, we present five validated models for predicting postoperative AKI (compared in table 2).[29–31] The validated models largely focus on patient factors; however, the two models developed by Kheterpal *et al.*[29,30] also incorporate surgical factors: (1) emergent surgery and (2) high-risk (or alternatively, intraperitoneal) surgery.

Finally, postoperative inpatient or ICU factors have been implicated in the development of late postoperative AKI, occurring more than 48 h after surgery. These factors commonly include but are not limited to sepsis, mechanical ventilation, acute lung injury, blood transfusion, fluid balance, urinary obstruction, and medications (diuretics, vasopressors, and nonsteroidal anti-inflammatory drugs [NSAIDs]).[2,34]

Age and Sex

The relationship between age and sex on the development of AKI remains unresolved,[35] with preclinical[36,37] and clinical[38] evidence suggesting female sex to be protective against AKI, while the KDIGO guidelines report female sex as a risk factor for AKI.[8] The discrepancy is hypothesized to result from age-related changes in female-associated hormones such as estrogen and progesterone leading to studies showing postoperative AKI

Table 2. Comparison of Validated Risk Models for Postoperative AKI

Population	Noncardiac Surgery	General Surgery	Orthopedic Surgery	Noncardiac Surgery	Cardiac Surgery
Patient factors	Age ≥ 59 yr	Age ≥ 56 yr	Age at operation	Age at operation	
					Female sex
	Body mass index ≥ 32 kg/m²			Body mass index	
		Male sex	Male sex		
			Higher ASA Physical Status	Higher ASA Physical Status	
			Lower estimated glomerular filtration rate	Preoperative estimated glomerular filtration rate	Preoperative serum creatinine
	Peripheral vascular occlusive disease				
	COPD (necessitating bronchodilator therapy)			Pulmonary circulation disorders	COPD
	Liver disease	Ascites		Liver disease	
		Diabetes mellitus (oral or insulin therapy)	Diabetes	Diabetes (complicated)	Insulin-dependent diabetes
		Active congestive heart failure		Congestive heart failure	Congestive heart failure
					Left ventricular ejection fraction < 35%; preoperative intraaortic balloon pump; previous cardiac surgery
		Renal insufficiency (mild or moderate)		Baseline chronic kidney disease severity	
				Coagulopathy	
				Weight loss	
				AIDS/HIV	
		Hypertension		Hypertension	
				Baseline MAP	
			Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use	Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use	
				Preoperative β-blocker	
			Polypharmacy		
				Anemia/preoperative hemoglobin	
Surgical factors	Emergent surgery	Emergency surgery		Emergent surgery	Emergency surgery
	High-risk surgery	Intraperitoneal surgery		Surgical body region	Type of surgery
				Institutional factors	
Anesthetic factors				General anesthesia	
				Expected anesthesia duration	
				Intraoperative hypotension	
Reference	29	30	31	32	33

AIDS, acquired immunodeficiency syndrome; AKI, acute kidney injury; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; MAP, mean arterial pressure.

risk being performed in older, postmenopausal populations.[35] After adjusting for other risk factors, Privratsky *et al*. demonstrated that younger females had the lowest odds of postoperative AKI, which increased with age.[35] Furthermore, preoperative hormone replacement therapy was not shown to modify the risk for postoperative AKI. Males had a greater risk for postoperative AKI, but that difference gradually narrowed as the patient aged, with no difference noted in the 86- to 90-yr-old age stratification.

Intraoperative Hemodynamic Goals

Consensus Guidelines

The kidney, specifically, the renal medulla, is susceptible to ischemia and hypoxia during periods of hypoperfusion, most commonly presenting as systemic arterial hypotension.[39] Whereas direct causal relationships between hypotension and AKI are yet to be definitively established, it is well-described that even brief periods of mean arterial pressure (MAP) less than 65 mmHg during noncardiac surgery are associated

with myocardial injury, AKI, and death.[39,40] In this context, the PeriOperative Quality Initiative consensus-building (POQI-3) consensus statement recommends maintaining an intraoperative MAP greater than 65 mmHg to potentially reduce the risk of postoperative AKI, with higher targets in patients with pre-existing hypertension.[2] Conversely, the PeriOperative Quality Initiative consensus review did not find sufficient evidence in noncardiac surgery to recommend a hypertensive blood pressure threshold above which blood pressure–lowering therapies should be initiated, but did determine that systolic pressures greater than 140 mmHg in cardiac surgery were associated with 30-day mortality. Guidelines are further hampered by the lack of standardized definitions for intraoperative hypotension.

Meta-analyses

A 2009 meta-analysis found that perioperative hemodynamic optimization with fluids and inotropes reduced postoperative renal injury.[41] This study was limited by significant heterogeneity in terms of (1) goals of optimization, (2) modality of optimization, (3) definition of AKI, (4) surgical type, and (5) risk stratification. Notably, the fluid-only subgroup (no inotropes) showed no reduction in kidney injury; however, it was not possible to ascertain whether fluid and inotropes work synergistically, or whether inotropes conferred the overall protective effect.

Randomized Controlled Trials Measuring Postoperative AKI in Noncardiac Surgery

In the Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) trial, Futier *et al.* found that individualized treatment (*i.e.*, maintaining systolic blood pressure within 10% of baseline value using a norepinephrine infusion) resulted in lower rates of postoperative organ dysfunction (a composite metric that included renal failure) after noncardiac surgery when compared to standard management (*i.e.*, maintaining systolic blood pressure greater than 80 mmHg or within 40% of baseline value using ephedrine boluses).[42] These findings have not been reproduced and contrast with another randomized trial showing no difference in a composite outcome consisting of major adverse cardiovascular events (MACE), AKI, and all-cause mortality between populations with target MAP greater than 75 mmHg compared to 60 mmHg.[43]

The PeriOperative ISchemic Evaluation-3 (POISE-3) trial was an international randomized controlled trial to compare a hypotension-avoidance *versus* a hypertension-avoidance strategy on major vascular complications after noncardiac surgery.[44,45] *Hypotension-avoidance* (target MAP, 80 mmHg or greater; antihypertensives for systolic blood pressure greater than 130 mmHg) and *hypertension-avoidance* (target MAP, 60 mmHg or greater; antihypertensives continued) strategies resulted in a similar incidence of major vascular complications.[44] As the primary outcome in POISE-3 did not include AKI, further research (including subanalysis of POISE-3 data)[46] is necessary to identify hemodynamic targets and modifications associated with renal protective effect.[45]

The ongoing, tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications (GUARDIAN trial) compares tight pressure management compared to routine pressure management on a composite of major perfusion-related complications (myocardial injury, stroke, nonfatal cardiac arrest, stage 2 to 3 AKI, sepsis, and death) in patients undergoing major noncardiac surgery.[47] Preliminary results demonstrate that tight blood pressure management with norepinephrine infusion decreases intraoperative hypotension, but delaying antihypertensive medications has little effect on postoperative blood pressure.[47]

Observational Studies

A retrospective multicenter study found that the impact of intraoperative hypotension on postoperative AKI varies based upon the patient's risk quartile.[32] Specifically, they assessed the relationship between duration of intraoperative hypotension (at absolute, MAP less than 50 mmHg, 50 to 54 mmHg, 55 to 59 mmHg, and 60 to 64 mmHg; and relative hypotension thresholds, MAP more than 40% below preinduction baseline, 30 to 40%, and 20 to 30%) and KDIGO stage 1, 2, or 3 AKI. They found 12,431 (9.0%) cases of postoperative AKI among 138,021 major noncardiac surgical procedures reviewed.[32] Major risk factors for postoperative AKI were anemia, preoperative estimated glomerular filtration rate, surgery type, American Society of Anesthesiologists Physical Status, and anesthesia duration (table 2). As risk increased, less severe intraoperative hypotension was associated with postoperative AKI. Among the lowest risk quartile, no hypotension range was associated with postoperative AKI. In patients with medium risk (quartile 2), only severe intraoperative hypotension (MAP less than 50 mmHg) was associated with increased postoperative AKI risk. Whereas, in patients with high (quartile 3) or highest (quartile 4) risk, even mild intraoperative hypotension (55 to 59 mmHg) was associated with postoperative AKI.

Another large, multicenter retrospective study by Chiu *et al.* found an increased risk of AKI (despite decreased duration of hypotension) when liberal use of vasopressors was employed at the expense of fluid resuscitation.[48]

Patient Blood Management

Although preoperative anemia has consistently been identified as a risk factor for postoperative AKI,[32,49–51] studies have *not* demonstrated that correcting anemia (through either transfusion or transfusion-sparing strategies) decreases the risk for AKI.[51] Specifically, a randomized controlled trial of patients undergoing elective cardiac surgery showed that neither intravenous ferric carboxymaltose nor oral iron

(administered for 3 to 8 weeks before surgery) improved (1) baseline hemoglobin, (2) intraoperative transfusion requirement, or (3) risk for postoperative AKI.[52] Furthermore, a large meta-analysis of cardiac surgery patients found that patients with preoperative anemia were greater than three times more likely to develop postoperative AKI than those in the nonanemic group, but failed to show an association between perioperative transfusion and mortality.[51]

In addition to not improving outcomes, transfusion may actually be associated with an increased risk for postoperative AKI. A retrospective study of more than 33,000 cardiac surgery patients demonstrated transfusion of packed red blood cells was associated with both mortality and postoperative renal failure.[53] The association between transfusion and postoperative morbidity may be due to a sicker patient population in the transfusion group that persists despite risk adjustment and propensity score matching.[53–55] Alternatively, components of blood products (*i.e.*, myeloid-related protein 14) have been linked to direct renal injury in animal models.[56]

Within the noncardiac surgery[57] and critically ill[58] population, evidence supports a restrictive approach to blood transfusion. The optimal transfusion strategy for the cardiac surgery population remains unresolved, with the Transfusion Requirements After Cardiac Surgery trial showing a restrictive transfusion strategy (hematocrit less than 24%) to be noninferior to a liberal transfusion strategy (hematocrit greater than 30%),[59] while the Transfusion Indication Threshold Reduction trial showed a higher 90-day mortality in the restrictive transfusion group (hemoglobin less than 75 g/l) compared to the liberal threshold group (hemoglobin less than 90 g/l).[59] More recently, the Transfusion Requirements in Cardiac Surgery III trial demonstrated a restrictive transfusion strategy was noninferior to a liberal transfusion strategy with respect to the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis, with less blood transfused.[60] The 2023 American Association of Blood Banks Guidelines recommend (1) a restrictive transfusion strategy (defined as less than 7 g/dl) for hospitalized adult patients who are hemodynamically stable, (2) a transfusion threshold of 7.5 g/dl in cardiac surgery, and (3) 8 g/dl in orthopedic surgery or for patients with pre-existing cardiovascular disease.[61]

Intraoperative Fluid Management

Balanced *versus* Saline Crystalloid Solutions

Saline (0.9% sodium chloride; "normal saline") has historically been the most commonly used intravenous crystalloid for intraoperative resuscitation and maintenance fluid therapy[62]; however, physiologically balanced crystalloids, like lactated Ringer's solution, more closely approximate the physiologic levels of sodium, potassium, and chloride found in plasma.[63] Because normal saline has a superphysiologic concentration of chloride (154 mM, compared to 94 to 111 mM in plasma),[64] hyperchloremic metabolic acidosis is a known consequence of normal saline administration, but whether this is of any clinical consequence is unresolved.[65,66]

A recent meta-analysis of randomized controlled studies on the use of balanced *versus* normal saline in the perioperative period demonstrated (1) uncertain effect on postoperative mortality (low certainty), (2) uncertain effect on need for renal replacement therapy (low certainty), and (3) improved postoperative acid–base status (moderate certainty).[66] Further studies are necessary in specific surgical populations. For example, the Saline *versus* Lactated Ringer's Solution: The Saline or Lactated Ringer's (SOLAR) trial of elective colorectal and orthopedic surgery patients found no difference in composite postoperative complications or AKI between patients receiving perioperative saline or lactated Ringer's solution.[67] However, balanced crystalloid improved postoperative electrolyte (lower chloride and higher bicarbonate) and acid–base (higher pH) status; the clinical implications of these changes remains unresolved.[66]

This builds upon evidence from the critically ill population, which showed a high probability that using balanced crystalloids reduces AKI compared to saline,[68] although evidence from key randomized trials has been conflicting.[64,69] Specifically, the Balanced Solutions in Intensive Care Study (BaSICS) did not show a difference in 90-day mortality among critically ill patients bolused with saline compared to balanced solutions.[69] This contrasts with the earlier Isotonic Solutions and Major Adverse Renal Events Trial (SMART), which showed balanced crystalloid use resulted in lower rate of death, new renal replacement, or persistent renal dysfunction.[64] Among *noncritically* ill emergency department patients in the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial, there was no difference in hospital-free days (primary outcome), but there was lower incidence of major adverse kidney events within 30 days (composite of death, new renal replacement therapy, and persistent renal dysfunction).[70]

Crystalloid *versus* Colloid

Whether colloids have a role in surgery has been debated and studied.[71] Colloids, specifically hydroxyethyl starch solutions, initially held promise as a way to minimize overall volume of fluids administered, but have been shown to be nephrotoxic in the intensive care setting.[72–74] While the nephrotoxic effect was not replicated in surgical populations,[71,75,76] strong evidence of coagulopathy, bleeding, and transfusion[77] prompted the U.S. Food and Drug Administration (Silver Spring, Maryland) to issue a black box warning in 2013 and the European Medicines Agency (Amsterdam, The Netherlands) to suspend marketing authorization in 2018.[78] Widespread use of the synthetic colloid hydroxyethyl starch waned behind mounting evidence of potential clinical harm[79]; however, whether this risk persists with human-derived albumin (the primary colloid replacement for hydroxyethyl starch) remained unresolved.[80]

Albumin is routinely utilized in cardiac surgery to prime the cardiopulmonary bypass circuit and for volume replacement, although evidence supporting such practice is limited or conflicting.[81] The randomized, double-blind, single-center Albumin in Cardiac Surgery (ALBICS) trial showed no difference in major adverse events (a composite including AKI) between cardiac surgery patients with albumin or lactated Ringer's solution use for cardiopulmonary bypass priming fluid and perioperative volume replacement,[82] suggesting that routine use of albumin did not provide any benefit for patients undergoing cardiac surgery with cardiopulmonary bypass.[80] A recent meta-analysis confirmed this finding, leading to the conclusion that albumin should be used restrictively in cardiac surgery.[81]

Data on the perioperative use of albumin is almost nonexistent outside of cardiac surgery. The Choosing Wisely in Anesthesiology Initiative stated that routine administration of colloid for volume resuscitation "without appropriate indication" is one of the top five "low-value" activities in the field of anesthesiology[83]; however, it did not give guidance on when albumin might be indicated. Ongoing research seeks to better define populations that may derive benefit. Albumin may have a limited role in specific surgical populations[80] including hepatorenal syndrome,[84–86] spontaneous bacterial peritonitis,[87,88] or after paracentesis in liver failure patients.[89–91]

Volume of Fluid

The major goals of intraoperative fluid resuscitations are optimizing intravascular volume to increase cardiac output and perfusion pressure in order to improve renal blood flow and glomerular function.[92] Excessive fluid has also been shown to be associated with AKI[93]; however, the cause-and-effect relationship between the two remains unclear.[84,94] A further complexity is that positive fluid balance can be caused by a combination of increased administration, which is potentially modifiable, and decreased urine output, which could only be addressed through renal replacement therapy.[94] Finally, the definitions of "liberal," "restrictive," and "traditional" fluid administration have evolved and can overlap across trials, requiring careful review of specific interventions when interpreting study results.

The Restrictive *versus* Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial demonstrated that restrictive fluid resuscitation (goal, net zero fluid balance) protocol had a significantly higher rate of AKI when compared to the group receiving liberal fluid resuscitation (goal, reflective of traditional practice).[95] This contrasts with the results from a randomized trial showing that restrictive fluid resuscitation (in combination with pre-emptive norepinephrine infusion) reduced postoperative complications (which included both renal failure and transient creatinine increase) and hospitalization after radical cystectomy and urinary diversion.[96] In light of this clinical evidence, providers need to recognize that both hypovolemia and hypervolemia may be associated with AKI and adopt personalized management guided by physiologic endpoints.[94] Assessment of euvolemia can be guided by judicious fluid challenges with frequent assessment of fluid responsiveness, hemodynamic homeostasis, and clinical signs of hypoperfusion. Intraoperative positional changes can function like a passive leg raise maneuvers, potentially revealing fluid responsiveness. Furthermore, assessment should prioritize dynamic markers (stroke volume, pulse pressure variation) rather static metrics (central venous pressure, pulmonary artery occlusion pressure)[92]—which have been shown to be an unreliable predictor of fluid responsiveness.[97]

Venous Congestion and Management of Central Venous Pressure

A variety of factors in the perioperative environment, including (1) positive pressure ventilation, (2) intravenous fluids, (3) transfusion, and (4) cardiopulmonary bypass, impact venous congestion and central venous pressure.[15] While optimal volume status remains a complex topic, venous congestion has been associated with cardiac surgery–associated AKI in patients from the Statin AKI Cardiac Surgery trial[15] and the Aortic To RAdial Pressure (ATRAP) Gradient Study.[98] Furthermore, venous congestion was found to more accurately predict AKI than arterial hypotension in the latter population,[98] although prospective studies are necessary to assess whether treatment strategies to alleviate venous congestion alter the development of postoperative AKI.

Intraoperative Hyperglycemia Control

Dysglycemia (hypoglycemia, hyperglycemia, and glycemic variability) is hypothesized to be associated with postoperative AKI through a variety of mechanisms including oxidative stress, increased inflammation, and endothelial dysfunction.[99] Diabetes is a well-established risk factor for AKI,[30] but more recent research has found a link between poor glycemic control in the perioperative period and postoperative AKI,[100,101] raising a question whether careful management of blood sugar during the perioperative period has a renal protective effect. Studies assessing the renoprotective effect of intensive glycemic control have found conflicting results, with some studies demonstrating a renoprotective effect[102–104] and others showing no advantage (or even a higher risk of death and stroke) to intensive (target, 81 to 108 mg/dl) compared to conventional (target, less than 180 mg/l) glycemic control.[105,106] Based upon these studies, the POQI-3 recommends treating hyperglycemia to a target blood glucose less than 180 mg/dl to reduce the risk of postoperative AKI.[2]

Potential Renoprotective Effect of Dexmedetomidine

The α_2-adrenoreceptor agonist dexmedetomidine has been associated with lower risk of AKI after cardiac surgery[107] and delayed graft function after renal transplantation.[107] The mechanism of this potential renoprotective effect has

not been fully resolved but is hypothesized to result from a combination of intrinsic anti-inflammatory properties, sympatholytic activity leading to reduction of renal vasoconstriction, and smooth muscle relaxation.[108] Larger multicenter trials are needed to confirm this renoprotective effect and to resolve the ideal dexmedetomidine dose and timing.[108]

Nephrotoxic Insults

Management of Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been hypothesized to increase the risk for AKI through a variety of mechanisms, including systemic hypotension, renal artery constriction, and interstitial nephritis.[109] Recommendations and practice for the management of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the perioperative period are conflicting. The American College of Cardiology (Bethesda, Maryland) and American Heart Association (Dallas, Texas) recommending continuing during noncardiac surgery,[110] while anesthesia groups routinely hold on the day of surgery due to concerns of intraoperative hypotension.[111] Subanalysis of the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) cohort found that withholding angiotensin-converting enzyme inhibitors or angiotensin receptor blockers before major noncardiac surgery was associated with a lower risk of death and postoperative vascular events, although this study was not designed to assess renal outcomes.[112] This contrasts with an earlier meta-analysis that did not demonstrate a difference in mortality, morbidity, and complications between patients who continued or held their angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the perioperative period.[113] In the largest prospective study to date in major elective noncardiac surgery, conducted by the Student Audit and Research in Surgery (STARSurg) Collaborative, withholding angiotensin-converting enzyme inhibitors or angiotensin receptor blockers did not protect against the development of postoperative AKI.[109] The POQI-3 consensus statement recommends restarting angiotensin-converting enzyme inhibitors or angiotensin receptor blocker therapy within the first 48 h postoperatively in patients, as long as the patient is hemodynamically stable and not exhibiting signs of postoperative AKI.[2]

Additionally, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can lead to a "functional" AKI (defined as an increase in serum creatinine). The prospective Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury (TRIBE-AKI) study demonstrated that the graded increase in functional AKI (continued angiotensin-converting enzyme inhibitors or angiotensin receptor blocker greater than held angiotensin-converting enzyme inhibitors or angiotensin receptor blocker greater than no angiotensin-converting enzyme inhibitors or angiotensin receptor blocker use) was not accompanied by "structural" AKI (no difference in AKI risk between the three exposure groups, as assessed by four different urinary biomarkers for AKI).[114] The results of a study can be dramatically altered based upon how AKI is defined (serum creatinine changes *vs.* biomarkers), and this discrepancy may be especially pronounced in patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. This study demonstrates that a rise in serum creatinine is not always accompanied by tissue damage (and tissue damage does not always result in rising serum creatinine, *i.e.*, subclinical AKI), highlighting one of the major limitations of serum creatinine as a biomarker.

Management of NSAIDs

NSAIDs have been used to effectively mitigate postoperative pain while decreasing the opioid requirement.[115] NSAIDs can adversely affect renal *via* prostaglandin mediated afferent arteriolar dilation, which causes reduced glomerular perfusion,[116] leading to acute interstitial nephritis. Drug-associated acute interstitial nephritis presents a cell-mediated immune response, characterized by acute loss of kidney function, interstitial infiltrates, edema, and tubulitis on biopsy (with relative sparing of glomerulus and vasculature).[117] Because of this risk, the Medicines and Healthcare Products Regulatory Agency (London, United Kingdom) has recommend that NSAIDs be avoided in hypovolemic patients[118]; however, best practices in low-risk patients remain unresolved.[2] A 2018 meta-analysis found that although NSAIDs led to a slight increase in serum creatinine, this was of unclear clinical significance, and no reliable conclusions could be drawn regarding the association between NSAIDs and renal replacement therapy, hospital length of stay, or death.[116] A secondary analysis of data from the Restrictive *versus* Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial found that intraoperative NSAID or cyclooxygenase-2 inhibitor use was significantly associated with increased postoperative AKI, supporting the need for a randomized trial to better define the risk–benefit balance of these perioperative analgesic adjuncts.[119] Emerging proteomic research sheds light on the molecular pathways, specifically differences in prostaglandin synthesis, driving NSAID-attributed AKI in the perioperative space.[120]

Other Potential Nephrotoxic Exposures

Nephrotoxic medication exposure represents one of the most common etiologies of AKI in hospitalized patients.[121] Antimicrobials (antivirals, antibiotics, and antifungals) have been implicated in impaired renal function through mechanisms ranging from acute interstitial nephritis to acute tubular necrosis.[122] A variety of strategies to mitigate this risk has been proposed including (1) adjusting the dose based upon creatinine clearance, (2) avoiding concomitant nephrotoxins, and (3) regular assessment of antibiotic necessity and duration.[122] Implementation of an electronic health

record screening and clinical decision support reduced the rate of AKI by 64% among noncritically ill children.[121]

Exposure to iodinated contrast media has been associated with acute injury in numerous historical studies,[123] leading many clinicians to avoid contrast in patients with reduced renal function.[124] Studies showing the association between contrast and AKI often lacked a control group of patients not exposed to contrast,[123] whereas more recent well-controlled observational studies suggest a much lower association between contrast exposure and AKI.[125–127] The American College of Radiology (Reston, Virginia) clarified the implied causal relationship between contrast media and AKI through the adoption of two new terms: (1) contrast-induced AKI and (2) contrast-associated AKI.[128] Contrast-associated AKI is defined as any AKI occurring within 48 h after the administration of contrast media, while contrast-induced AKI is the subset of cases that can be causally linked to the contrast exposure.[124] While the incidence of contrast-induced AKI is markedly lower than that of contrast-associated AKI,[124] the actual risk remains unresolved, with some studies showing no elevated risk for contrast-induced AKI regardless of baseline renal function[126] and others showing risk only at severely reduced renal function.[127] The primary risk factor for contrast-associated AKI remains baseline estimated glomerular filtration rate, with diabetes mellitus, nephrotoxic exposure, hypotension, and hypovolemia conferring additional risk.[124] From a pragmatic perspective, given these uncertainties, renal risk alone should not contraindicate truly necessary imaging.

In addition to the previously described patient-specific risk factors, procedure-specific factors impact the development of contrast-associated AKI. For example, percutaneous coronary interventions (particularly in ST-Elevation Myocardial Infarction [STEMI] patients) are particularly susceptible to AKI due to contrast exposure, reduced perfusion secondary to transient hypotension or reduced cardiac output, and high baseline patient risk due to comorbidities.[129] Intraarterial contrast places the patient at higher risk than intravenous contrast administration, which has improved with decreasing osmolar concentration of intravenous contrast.[130] The volume and osmolarity of the of contrast media represent two modifiable risk factors.[129,131]

Protocolized Management

The KDIGO guidelines make a number of recommendations for minimizing AKI, including (1) avoidance of nephrotoxic agents, (2) discontinuation of angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers for 48 h after surgery, (3) close monitoring of serum creatinine and urine output, (4) avoidance of hyperglycemia, (5) avoidance of radiocontrast, (6) hemodynamic monitoring with a pulse index continuous cardiac output catheter, and (7) algorithm-based optimization of volume and hemodynamic status.[8,132] Meersch *et al.* found that a therapeutic bundle derived from these KDIGO recommendations significantly reduced the rate of cardiac surgery–associated AKI (55.1% *vs.* 71.7%; absolute risk reduction, 16.6; 95% CI, 5 to 27.9%; $P = 0.004$) within 72 h compared to standard care (MAP greater than 65 mmHg and central venous pressure between 8 and 10 mmHg).[132] This contrasts with a more recent study from Shen *et al.* demonstrating that an enhanced recovery after surgery protocol consisting of balanced fluid management, flexible use of vasoactive drugs, and multimodal analgesia containing NSAIDs was safe but did not impact incidence of postoperative AKI.[133] The bundled interventions limit speculation on the contribution of any single measure.

Treatment

Stage-based Treatment Approach

Because advances in the treatment of postoperative AKI have been limited,[6,7] management in the perioperative period has traditionally focused on prevention and diagnosis. Once postoperative AKI develops, supportive management (*i.e.*, preventing ongoing renal insult through removal of nephrotoxic agents and optimized renal perfusion through fluids and vasopressors) is the mainstay of therapy.[134]The 2012 KDIGO guidelines for the management of AKI recommend a stage-based treatment approach.[7,135] For stage 1 AKI or patients at high risk for AKI, primary management goals include identifying the likely cause of AKI and avoiding secondary insults where possible (such as administration of NSAIDs or other nephrotoxic medications when alternatives are available).[7] In addition, hemodynamic optimization to ensure adequate kidney perfusion is an important goal, although the guidelines do not provide specific hemodynamic targets. Two single-center randomized controlled trials (one in cardiac surgery and one in noncardiac surgery patients) demonstrated significant reductions in postoperative AKI with a bundled care approach including target MAP 65 mmHg or greater.[136,137] Notably, a meta-analysis suggested that protocolized approaches to hemodynamic optimization are associated with reduced risk of AKI overall despite differences in specific targets.[41]

In patients who progress to stage 2 AKI, adjusting drug dosages to account for glomerular filtration and careful attention to volume input or output become important. Stage 3 AKI is associated with acid–base imbalance, altered electrolyte levels, and accumulation of uremic toxins.[7] Decisions on the need for intensive care and initiation of kidney replacement therapy require expertise in nephrology or critical care medicine and should be considered early in disease progression.[135]

Phase of care, monitoring, and follow-up can vary greatly depending on the severity of disease. The KDIGO clinical practice guidelines recommend that all patients diagnosed with AKI are evaluated at 3 months to screen for new or progressive chronic kidney disease,[135,138] while the Acute Disease Quality Initiative and PeriOperative Quality Initiative recommend all postoperative patients with AKI or acute kidney

disease have a kidney health assessment within 30 days of hospital discharge.[2] As morbidity and mortality increase with severity of AKI (and in patients without renal recovery), these factors should inform the frequency and nature of follow-up.[2] Management of AKI during the period of inpatient hospitalization provides an opportunity to prevent or delay progression of AKI to chronic kidney disease.[138] Patients requiring acute renal replacement therapy (or necessitate continuous renal replacement therapy due to hemodynamic instability) should be managed in the ICU.[139] Furthermore, a variety of critical conditions associated with AKI including shock, sepsis, acid–base imbalance, and respiratory failure secondary to fluid overload require intensive care. The KDIGO management guidelines recommend considering ICU admission beginning at stage 2 AKI.[135]

Prevention of AKI

Diuretics may be used to manage volume overload secondary to AKI and increase potassium excretion.[8] Administration of loop diuretics has been shown to reverse oligo-anuria, revealing patients with less severe renal injury or adequate renal reserve,[140] but has not been shown to prevent AKI, need for renal replacement therapy, or overall mortality.[141,142] Judicious fluid administration combined with loop diuretics (*i.e.*, "matched hydration") may increase tubular flow of filtrate without volume depletion and associated renal hypoperfusion[143–145]; however, further randomized control trials are necessary before this strategy can be broadly recommended in the prevention of postoperative AKI.[141]

Despite initially promising studies,[146,147] neither preoperative aspirin nor clonidine reduced the risk of postoperative AKI in the POISE-2 randomized trial of noncardiac surgery patients.[23] Dexamethasone potentially attenuates the systemic inflammatory response to cardiopulmonary bypass and reducing inflammatory mediators, but the Dexamethasone in Cardiac Surgery (DECS) trial and the Steroids in Cardiac Surgery (SIRS) trial failed to support prophylactic use of steroids during cardiac surgery.[148,149] Finally, a meta-analysis found no evidence that N-acetylcysteine improved renal outcomes after major surgery[150]; therefore, the KDIGO management guidelines recommend against using oral or intravenous N-acetylcysteine for prevention of postsurgical AKI.[135]

Management of Postoperative AKI

The Acute Disease Quality Initiative and PeriOperative Quality Initiative consensus report recommends determining and resolving the underlying cause of postoperative AKI.[2] Mainstays of management include removal or avoidance of nephrotoxic exposure and hemodynamic optimization. Renal perfusion can be maintained through a combination of fluids and vasopressors, with protocol-based management to prevent worsening AKI in high-risk perioperative patients. Diuretics should not be used in the treatment of AKI, except to manage volume overload.[2] A number of agents including dopamine, fenoldopam, atrial natriuretic peptide, insulin-like growth factor-1, and diuretics have failed to improve the course of AKI and do not have a role in the management of AKI.[2,8]

Timing and Indications for Renal Replacement Therapy

Renal replacement therapy is used only if there is a specific indication, like severe acidosis, hyperkalemia, uremia, or inability to manage volume status with diuretics.[2,8] The Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial showed no evidence of benefit and higher risk for dependence at 90 days when renal replacement therapy was initiated early for postoperative AKI compared to conservative management.[151] The optimal timing and indications for renal replacement therapy remain unresolved and should be carefully weighed on an individual basis.[1] Absolute indications for renal replacement therapy include (1) symptoms or signs of uremia (*i.e.*, pericarditis, bleeding, or encephalopathy), (2) pulmonary edema resistant to diuretics, (3) refractory hyperkalemia (greater than 6.5 mM, rapidly increasing, or associated with cardiac arrhythmias), (4) metabolic acidosis (pH less than 7.2), or (5) intoxication with dialysable drug or toxin.[152,153] Relative indications are (1) organ dysfunction impacted by either fluid overload or from the AKI; (2) administration of large volumes of fluid (*i.e.*, blood transfusion); (3) solute burden such as from tumor lysis syndrome, rhabdomyolysis, or hemolysis; and (4) oligo-anuria due to severe AKI with low probability of rapid renal recovery.[152]

Special Populations

Cardiac Surgery

The incidence of AKI after cardiac surgery ranges from 15 to 30%.[18,154] Even patients who fully recovered renal function after developing AKI had a significantly higher mortality than those not developing AKI.[155] The increased incidence of AKI in cardiac surgery patients can be attributed to both the unique stress profile of the procedure (*e.g.*, cardiopulmonary bypass impairing autoregulatory mechanisms and inducing and inflammatory response, hemodilution, and atheroembolic events associated with bypass cannulation and the surgical technique) and the risk profile of the patient population. A variety of risk prediction models for AKI after cardiac surgery have been developed including the Cleveland Clinic Score,[33] the Mehta Score,[156] and the Simplified Renal Index.[157] Intraoperative risk factors include cardiopulmonary bypass, blood transfusion, proteinuria, urgent surgery, reoperation, and preoperative intra-aortic balloon pump.[49,158,159] Patients undergoing valvular surgery have a higher incidence of cardiac surgery–associated AKI than those undergoing coronary artery

bypass graft surgery.[49,160] Strategies for prevention and mitigation of cardiac surgery–associated AKI have been comprehensively reviewed,[155,161] and include implementation of the "KDIGO bundle of care,"[132] goal-directed oxygen delivery while on cardiopulmonary bypass,[162,163] and a restrictive transfusion threshold.[164]

The Vasopressin *versus* Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS) trial found that patients receiving vasopressin as a first-line agent had lower incidence of moderate to severe AKI than those receiving norepinephrine,[165] and dobutamine reduced cardiac surgery–associated AKI when implemented as a part of a "bundle of care" approach.[132,166] Further research is necessary on the optimal and mitigation strategies and hemodynamic targets.

The Society of Thoracic Surgeons (Chicago, Illinois) definition for postoperative acute renal failure essentially only includes stage 3 (or dialysis-requiring) AKI.[167] While other studies apply the KDIGO criteria after cardiac surgery,[168–170] Society of Thoracic Surgeons database reporting notably focuses on this acute renal failure definition.

Cirrhosis

Diagnostic criteria relying on serum creatinine can overestimate kidney function in cirrhotic patients, and bilirubin can decrease the accuracy of creatinine assays.[171] A joint consensus statement from the International Club of Ascites (ICA) and the Acute Disease Quality Initiative recommends defining AKI in patients with cirrhosis using the KDIGO criteria, while using the lowest serum creatinine value up to 12 months before.[172] In addition to AKI meeting the KDIGO definition, a diagnosis of hepatorenal syndrome, AKI requires (1) cirrhosis with ascites, (2) absence of improvement in serum creatinine and/or urine output within 24 h after adequate volume resuscitation, and (3) absence of an alternative explanation for the primary cause of AKI.[171,172] ICA modifications to KDIGO have shown to accurately predict 30-day mortality, length of hospital stay, and organ failure.[173] However, because automated algorithms calculate and surgical registries curate AKI outcomes using KDIGO standard criteria, the unmodified KDIGO definition has been employed in studies in the liver transplant population without issue.[28]

Renal Transplant

Delayed graft function, typically defined as dialysis requirement within 1 week of transplant, is a manifestation of AKI attributable to the transplant process.[174] Delayed graft function occurs in about one of five transplants, with incidence in deceased donor transplants as high as 40%,[175] and is associated with clinical outcomes including acute rejection,[176] poor graft survival,[174] and increased mortality.[177,178] Furthermore, delayed graft function exacts a significant economic burden, increasing transplant cost by more than $18,000, length of hospitalization by 6 additional days, and ICU stay by 2 days.[175,179,180] Despite improved understanding of the pathophysiology leading to delayed graft function, including the molecular mechanism of ischemia–reperfusion injury and allograft immunogenicity,[177] the incidence of delayed graft function has continued to rise (presumably due to increased cold ischemia time resulting from changes in the Kidney Allocation System).[175]

Traditional risk factors[181] for delayed graft function can be divided into (1) donor factors (age, sex, body mass index, *etc.*), (2) recipient factors (age, race, sex, comorbidities, *etc.*), (3) graft factors (cold ischemia time, human leukocyte antigens or ABO incompatibility, deceased donor compared to living donor, and donation after cardiac death compared to donation after brain death), and (4) surgical factors (right nephrectomy, laparoscopic approach for donor nephrectomy, *etc.*).[182–184] Improved risk stratification informs management decisions (for example, invasive monitoring in high-risk patients) and organ allocation; however, characterized risk factors are mostly nonmodifiable. The intraoperative and early ICU periods remain an understudied source of outcome variation and represent a window where early intervention could modify the clinical trajectory.

Emerging Science

Biomarkers

Despite standardization of AKI criteria, diagnosis remains dependent on changes in serum creatinine and urine output.[185] A major limitation of serum creatinine as an AKI biomarker is that it does not increase until substantial parenchymal injury has occurred. This time "lag" prevents recognition of renal injury during the time window, when early intervention can alter the clinical course.[186] Furthermore, functional biomarkers like serum creatinine are altered by a variety of overlapping processes, independent of renal injury (like fluid overload, malnutrition, and muscle wasting).[186,187] Significant effort has been devoted on identifying and validating novel biomarkers for AKI in the perioperative period that may reflect the specific process of nephron injury and enable earlier detection of AKI.[185]

Biomarkers can be categorized into multiple overlapping classification schema: (1) blood *versus* urine, (2) anatomic location (glomerulus, proximal tubule, loop of Henle, and distal tubule), and (3) functional mechanism (injury, inflammation, and repair or fibrosis).[185] Injury biomarkers are released from injured kidney cells (analogous to troponin release from injured myocardial cells during an infarction), potentially providing a more sensitive and specific marker of AKI than blood urea nitrogen and serum creatinine.[188] The *injury* biomarkers, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and liver fatty acid–binding protein, are early markers of renal tubular injury and potentially identify AKI during the "blind window" before rise in serum creatinine or BUN.[188] *Inflammatory* biomarkers, interleukin-18, tumor necrosis factor receptor-1 (TNFR-1), tumor

Table 3. Comparison of Common AKI Biomarkers

Biomarker	Source	Classification	Initial Rise	Peak	Sensitivity	Specificity	Reference
Creatinine	Serum	Filtration	10 h	> 48 h	37 (91)*	83 (40.8)*	201,202
CysC	Plasma	Filtration	4 h	24 h	44–82	92–95	203–205
IL-18	Urine	Inflammatory	6 h	12 h	68	80	200,206
KIM-1	Urine	Injury	12 h	24 h	76	79	198,200,207–209
L-FABP	Urine	Injury	2 h	12 h	70	81	200,210
NGAL	Urine	Injury	2 h	6 h	77	81	197,200
[TIMP-2] × [IGFBP7]	Urine	Stress	4–6 h	10 h	68	74	200,204,211

*Serum creatinine is a late marker for AKI (does not peak for 48–72 h after renal injury) and has poor sensitivity for postoperative AKI (since serum creatinine remains stable until more than 50% of nephrons are impacted).[212] The KDIGO definition for AKI has historically been treated as the accepted standard or reference, complicating sensitivity or specificity calculations of the serum creatinine biomarker.[213] Additionally, focusing on the serum creatinine component of the KDIGO criteria (while ignoring urine output) underestimates stage 2 or greater AKI and decreases sensitivity.[214]

AKI, acute kidney injury; CysC, cystatin C; IGFBP7, insulin like growth factor binding protein 7; KDIGO, Kidney Disease: Improving Global Outcomes; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated with lipocalin; IL-18, interleukin-18; L-FABP, liver fatty acid-binding protein; TIMP-2, tissue inhibitor of metalloproteinases 2.

necrosis factor receptor-2 (TNFR-2), and osteopontin, are activated and recruited as an early response to kidney injury, and hold promise (in combination with other biomarkers) of predicting prognosis and progression of postoperative AKI.[189–191] Additionally, specific *inflammatory* markers, tumor necrosis factor-α (TNF-α) and interleukin-9, can be used to differentiate acute interstitial nephritis from other causes of AKI.[192] After injury and inflammation, a tightly regulated reparative process occurs. Biomarkers associated with *repair* (epidermal growth factor and chitinase 3-like 1) and *fibrosis* (transforming growth factor-β [TGF-β]), monocyte chemoattractant protein 1, and type III procollagen peptide can be leveraged to predict renal recovery and interstitial fibrosis or tubular atrophy.[193]

Injury biomarkers rise at different rates, with each having a characteristic injury response curve (analogous to the sequential rise of myoglobin, troponin I, creatine phosphokinase, and lactate dehydrogenase after myocardial injury).[194] For example, urinary neutrophil gelatinase-associated lipocalin begins to rise within 2 h and peaks within 6 h after surgery.[195–197] This compares to kidney injury molecule-1, which typically rises within 12 h, peaking around 24 h.[197,198] A comparison of the time course for novel AKI biomarkers can be found in table 3.

Combining multiple biomarkers enables improved risk prediction (quantified by discrimination and net reclassification improvement) earlier in the disease course, when interventions are more likely to impact disease trajectory.[195] Nephrocheck (bioMerieux, France), a test that combines urinary tissue inhibitor of metalloproteinases 2 and insulin like growth factor binding protein 7, was approved by the Food and Drug Administration as the first biomarker for AKI in 2014. The sensitivity and specificity of all biomarkers depend on (1) the temporal relationship between renal injury and when the sample is drawn, (2) the diagnostic threshold selected, and (3) the AKI population (critically ill, cardiac surgery, *etc.*). Plasma biomarkers demonstrate better discrimination for early postoperative AKI (compared to urine biomarkers) even when normalized to urinary creatinine and injury biomarkers had better predictive ability than either stress or inflammatory biomarkers.[199,200] Across all populations and AKI etiologies, serum and urine neutrophil gelatinase-associated lipocalin had the best diagnostic accuracy (table 3); however, performance was more limited in surgical populations (with neutrophil gelatinase-associated lipocalin/creatine performing best in this population).[200]

Continued development, validation, and integration of biomarker panels will enable earlier, more accurate diagnosis of AKI.[192] More recently, an independent dose–response association was seen between the level of urinary biomarkers (interleukin-18, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, liver fatty acid–binding protein, and albumin) and duration of AKI in the TRIBE-AKI cardiac surgery cohort.[215] Urinary epidermal growth factor and monocyte chemoattractant protein 1 predict which AKI patients are likely to develop chronic kidney disease after cardiac surgery.[216] In addition to predicting AKI progression and AKI–to–chronic kidney disease transition, novel biomarkers can impact the management of AKI[185]—for example, (1) guiding diuresis in patients with acute decompensated heart failure[217] and (2) triggering implementation of the KDIGO care bundle after major abdominal surgery.[137] Ongoing research will define meaningful subgroups using a combination of genomic data, transcriptomics, and biomarkers.[218] Furthermore, advanced analytical techniques will integrate molecular signatures from multiple biomarkers, establish unbiased predictive cutoff values, and provide insight into the pathology and progression of renal disease.[185]

Genetics

While the genetic contribution of chronic kidney disease has been well characterized,[219] the genetics of AKI remains poorly understood. Most studies on the genetic underpinnings of AKI have employed a candidate gene approach and failed to identify contributory variants consistently.[220] A genome-wide association study of AKI in a general

hospitalized population (mixture of different AKI risk factors including surgery, sepsis, and nephrotoxic medications) failed to identify any variants at the level of genome-wide significance ($P < 5 \times 10^{-8}$), but did report two novel variants adjacent to the dispatched RND transporter family member 1 (*DISP1*) and Toll-like receptor 5 (*TLR5*) genes at a lower suggestive threshold.[221] Genome-wide association studies focused on postoperative AKI[222] and cardiac surgery–associated AKI[223–226] have found very few significant associations, and these associations were not consistently replicated across studies. Additionally, a polygenic score that summarizes the genetic burden across the whole genome into a single number that can be used in disease risk modeling was not associated with cardiac surgery–associated AKI.[225] These may be because cardiac surgery–associated AKI is only minimally influenced by baseline genetics, and clinical risk factors play a more influential role in the development and pathogenesis.[225] The expansion of biobanks will enable greater statistical power on a larger, more diverse population.[225] Future studies may also identify subpopulations where genetics may exert disproportionate influence (for example, stratified by patient risk or stage of AKI).

Future Directions

Although preservation of renal perfusion is fundamental to AKI prevention and management,[7] the optimal strategy to ensure this remains unresolved. Ongoing research will provide insight into optimal (1) choice of vasopressors or inotropes, (2) fluid management, and (3) hemodynamic or oxygenation goals for targeted management,[7,155] and will likely require a personalized or precision-medicine approach. In addition to understanding interventions to optimize renal perfusion, more research on the temporal relationship between each of these exposures and renal injury is necessary. For example, intraoperative hypotension has traditionally been evaluated over the entire course of the procedure.[39] Future studies that employ a more nuanced definition for hypotension could overcome such limitations while providing insight into the specific mechanism and timing between perfusion and AKI. Furthermore, the risk–benefit balance between nephrotoxic exposures, like NSAIDs and intravascular contrast, remains an area of active research. The incidence of contrast-associated AKI and effective interventions in high-risk patients remain areas of controversy and active research.[155] Advances in analytical and predictive algorithms, including machine-learning and clinical decision support, will enable more accurate prediction and stratification of patients at risk for AKI.

Many studies have focused on the serum creatinine–based diagnostic criteria, while less attention has been paid to prognostic implications and management of oliguria.[2,227] Despite key limitations, serum creatinine remains the standard biomarker for AKI in perioperative practice.[10] Advances in biomarkers may enable improved sensitivity, earlier detection, prognostic insight, and more precise classification. The management of AKI is largely supportive (prevent ongoing renal insult and optimize renal perfusion),[134] with the optimal timing and indications for renal replacement therapy unresolved.[1] Proposed treatments for AKI, including dopamine, fenoldopam, aspirin,[23] steroids,[149] and ischemic preconditioning,[228] have not been found to alter the course of disease; however, prevention and treatment modalities remain key areas for future research.

Conclusions

Perioperative AKI has been consistently associated with long-term morbidity,[1] mortality,[2] and healthcare costs,[3] even among patients with complete renal recovery.[4] Treatment options for postoperative AKI are limited,[6,7] so perioperative management has traditionally focused on prevention and diagnosis. The KDIGO criteria, currently used to define AKI,[8] rely on changes in serum creatinine and absolute urine output to provide an easy-to-interpret, objective, and validated approach useful for epidemiologic studies; however, this definition has notable limitations, including a susceptibility to be influenced by nonrenal factors and a time lag between nephron injury and rise in serum creatinine.[8] AKI represents a clinical syndrome, rather than a single disease, with commonly implicated mechanisms including (1) oxido-inflammatory stress, (2) renal hypoperfusion, (3) endogenous or exogenous nephrotoxins, and (4) iatrogenic causes. Risk factors for postoperative AKI are divided into (1) patient-related, (2) surgery-related, (3) anesthetic-related, and (4) ICU-related risk factors. Recent studies have attempted to integrate anesthetic factors into risk assessment.[32] Notably, characterizing hypotension is complicated by nonstandardized definitions and baseline risk. A variety of strategies for prevention and mitigation of postoperative AKI have been proposed and include preservation of renal perfusion, avoidance of nephrotoxic exposure, implementation of bundles of care, goal-directed oxygen delivery, and a restrictive transfusion threshold. Ongoing research will provide insight into optimal choice of vasopressors or inotropes, fluid management, and hemodynamic or oxygenation goals for targeted management, and will likely require a personalized or precision-medicine approach. Continued development, validation, and integration of biomarker panels will enable earlier, more accurate diagnosis of AKI.

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