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

Nicholas J. Douville, M.D., Ph.D., Michael Mathis, M.D., Sachin Kheterpal, M.D., M.B.A., Michael Heung, M.D., Jennifer Schaub, M.D., Abhijit Naik, M.B.B.S., Matthias Kretzler, M.D.

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]

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

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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.
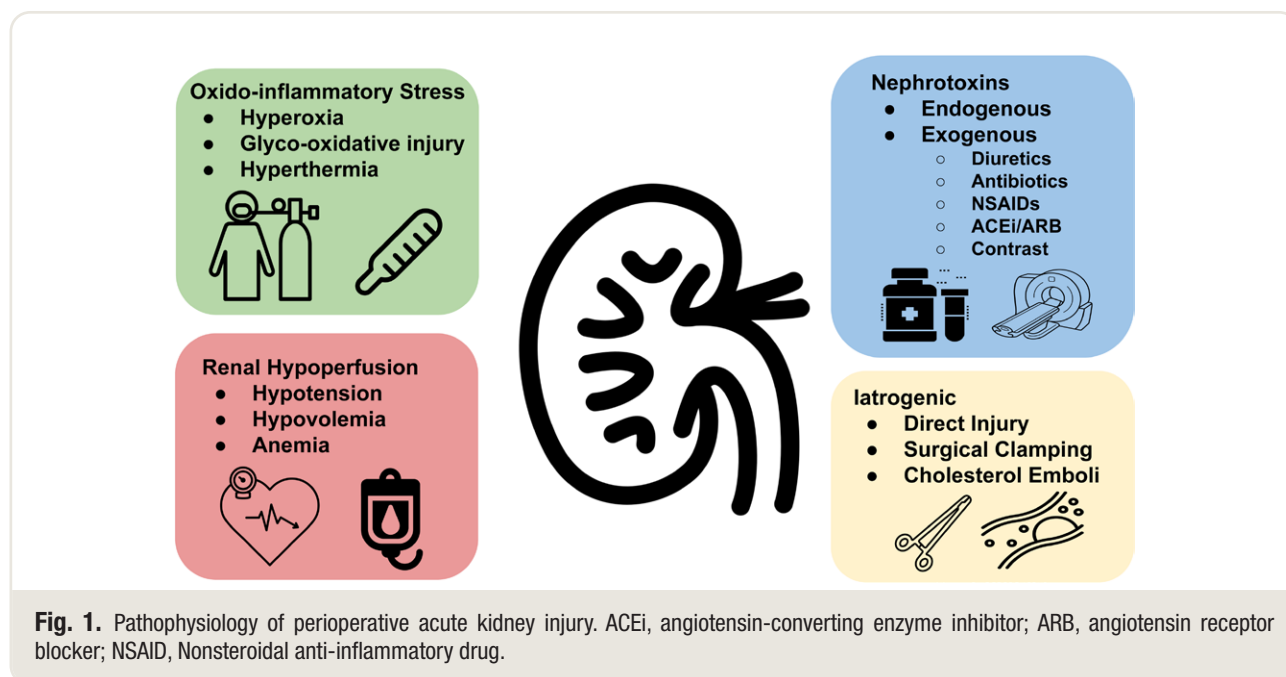
AKI due to a combination of patient and surgical risk factors. Although the incidence across all vascular procedures is estimated to be as high as 49%,[3] the incidence differs dramatically based on specific procedure. For example, procedures on the lower extremities have a relatively low incidence of 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	Preoperative serum creatinine
			Lower estimated glomerular filtration rate	Preoperative estimated glomerular filtration rate	
	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
Anesthetic factors				Institutional 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 non-existent 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.

Research Support

Correspondence

Address correspondence to Dr. Douville: Department of Anesthesiology, University of Michigan, 1H247 UH, SPC 5048, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109-5048. ndouvill@med.umich.edu.

References

1. O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR: Incidence and associations of acute kidney injury after major abdominal surgery. Intensive Care Med 2016; 42:521–30
2. Prowle JR, Forni LG, Bell M, et al.: Postoperative acute kidney injury in adult non-cardiac surgery: Joint consensus report of the Acute Disease Quality Initiative and PeriOperative Quality Initiative. Nat Rev Nephrol 2021; 17:605–18
3. Hobson C, Lysak N, Huber M, Scali S, Bihorac A: Epidemiology, outcomes, and management of acute kidney injury in the vascular surgery patient. J Vasc Surg 2018; 68:916–28
4. Tian J, Barrantes F, Amoateng-Adjepong Y, Manthous CA: Rapid reversal of acute kidney injury and hospital outcomes: A retrospective cohort study. Am J Kidney Dis 2009; 53:974–81
5. Kork F, Balzer F, Spies CD, et al.: Minor postoperative increases of creatinine are associated with higher mortality and longer hospital length of stay in surgical patients. Anesthesiology 2015; 123:1301–11
6. Gumbert SD, Kork F, Jackson ML, et al.: Perioperative acute kidney injury. Anesthesiology 2020; 132:180–204
7. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders H-J: Acute kidney injury. Nat Rev Dis Primers 2021; 7:52
8. Khwaja A: KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120: c179–c184
9. Doi K, Yuen PST, Eisner C, et al.: Reduced production of creatinine limits its use as marker of kidney injury in sepsis. J Am Soc Nephrol 2009; 20:1217–21
10. Slocum JL, Heung M, Pennathur S: Marking renal injury: Can we move beyond serum creatinine? Transl Res 2012; 159:277–89
11. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative Workgroup: Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:R204–12
12. Mehta RL, Kellum JA, Shah SV, et al.; Acute Kidney Injury Network: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11:R31
13. Schurle A, Koyner JL: CSA-AKI: Incidence, epidemiology, clinical outcomes, and economic impact. J Clin Med Res 2021; 10:5746
14. Chawla LS, Bellomo R, Bihorac A, et al.; Acute Disease Quality Initiative Workgroup 16: Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol 2017; 13:241–57
15. Lopez MG, Shotwell MS, Morse J, et al.: Intraoperative venous congestion and acute kidney injury in cardiac surgery: An observational cohort study. Br J Anaesth 2021; 126:599–607
16. Boyer N, Eldridge J, Prowle JR, Forni LG: Postoperative acute kidney injury. Clin J Am Soc Nephrol 2022; 17:1535–45

17. Lewington AJP, Cerdá J, Mehta RL: Raising awareness of acute kidney injury: A global perspective of a silent killer. Kidney Int 2013; 84:457–67

18. Hu J, Chen R, Liu S, Yu X, Zou J, Ding X: Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2016; 30:82–9

19. Lei S-H, Guo G-F, Yan T, Zhao B-C, Qiu S-D, Liu K-X: Acute kidney injury after general thoracic surgery: A systematic review and meta-analysis. J Surg Res 2023; 287:72–81

20. Beek SC van, Legemate DA, Vahl A, et al.: Acute kidney injury defined according to the "Risk," "Injury," "Failure," "Loss," and "End-stage" (RIFLE) criteria after repair for a ruptured abdominal aortic aneurysm. J Vasc Surg 2014; 60:1159–67, 1167.e1

21. Abelha FJ, Botelho M, Fernandes V, Barros H: Determinants of postoperative acute kidney injury. Crit Care 2009; 13:R79

22. Biteker M, Dayan A, Tekkeşin AI, et al.: Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery. Am J Surg 2014; 207:53–9

23. Garg AX, Kurz A, Sessler DI, et al.; POISE-2 Investigators: Perioperative aspirin and clonidine and risk of acute kidney injury: A randomized clinical trial. JAMA 2014; 312:2254–64

24. Perkins ZB, Captur G, Bird R, Gleeson L, Singer B, O'Brien B: Trauma induced acute kidney injury. PLoS One 2019; 14:e0211001

25. Haines RW, Lin S-P, Hewson R, et al.: Acute kidney injury in trauma patients admitted to critical care: Development and validation of a diagnostic prediction model. Sci Rep 2018; 8:3665

26. Kim M, Brady JE, Li G: Variations in the risk of acute kidney injury across intraabdominal surgery procedures. Anesth Analg 2014; 119:1121–32

27. Lima EQ, Zanetta DMT, Castro I, et al.: Risk factors for development of acute renal failure after liver transplantation. Ren Fail 2003; 25:553–60

28. Berkowitz RJ, Engoren MC, Mentz G, et al.: Intraoperative risk factors of acute kidney injury following liver transplantation. Liver Transpl 2022; 28:1207–23

29. Kheterpal S, Tremper KK, Englesbe MJ, et al.: Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 2007; 107:892–902

30. Kheterpal S, Tremper KK, Heung M, et al.: Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. Anesthesiology 2009; 110:505–15

31. Bell S, Dekker FW, Vadiveloo T, et al.: Risk of postoperative acute kidney injury in patients undergoing orthopaedic surgery––Development and validation of a risk score and effect of acute kidney injury on survival: Observational cohort study. BMJ 2015; 351:h5639

32. Mathis MR, Naik BI, Freundlich RE, et al.; Multicenter Perioperative Outcomes Group Investigators: Preoperative risk and the association between hypotension and postoperative acute kidney injury. Anesthesiology 2020; 132:461–75

33. Thakar CV, Arrigain S, Worley S, Yared J-P, Paganini EP: A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005; 16:162–8

34. Li S, Wang S, Priyanka P, Kellum JA: Acute kidney injury in critically ill patients after noncardiac major surgery: Early versus late onset. Crit Care Med 2019; 47:e437–44

35. Privratsky JR, Fuller M, Raghunathan K, et al.: Postoperative acute kidney injury by age and sex: A retrospective cohort association study. Anesthesiology 2023; 138:184–94

36. Kang KP, Lee JE, Lee AS, et al.: Effect of gender differences on the regulation of renal ischemia-reperfusion-induced inflammation in mice. Mol Med Rep 2014; 9:2061–8

37. Kher A, Meldrum KK, Wang M, Tsai BM, Pitcher JM, Meldrum DR: Cellular and molecular mechanisms of sex differences in renal ischemia–reperfusion injury. Cardiovasc Res 2005; 67:594–603

38. Neugarten J, Golestaneh L: Female sex reduces the risk of hospital-associated acute kidney injury: A meta-analysis. BMC Nephrol 2018; 19:314

39. Lankadeva YR, May CN, Bellomo R, Evans RG: Role of perioperative hypotension in postoperative acute kidney injury: A narrative review. Br J Anaesth 2022; 128:931–48

40. Sessler DI, Bloomstone JA, Aronson S, et al.; Perioperative Quality Initiative-3 Workgroup: Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019; 122:563–74

41. Brienza N, Giglio MT, Marucci M, Fiore T: Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med 2009; 37:2079–90

42. Futier E, Lefrant J-Y, Guinot P-G, et al.; INPRESS Study Group: Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: A randomized clinical trial. JAMA 2017; 318:1346–57

43. Wanner PM, Wulff DU, Djurdjevic M, Korte W, Schnider TW, Filipovic M: Targeting higher intraoperative blood pressures does not reduce adverse cardiovascular events following noncardiac surgery. J Am Coll Cardiol 2021; 78:1753–64

44. Marcucci M, Painter TW, Conene D, et al.; POISE-3 Trial Investigators and Study Group: : Hypotension-avoidance versus hypertension-avoidance strategies in noncardiac surgery. Ann Intern Med 2023; 176:605–15

45. Marcucci M, Painter TW, Conen D, et al.; POISE-3 Trial Investigators and Study Groups: Hypotension-avoidance versus hypertension-avoidance strategies in

noncardiac surgery: An international randomized controlled trial. Ann Intern Med 2023; 176:605–14

46. Garg AX, Cuerden M, Aguado H, et al.: Effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy on the risk of acute kidney injury: A clinical research protocol for a substudy of the POISE-3 randomized clinical trial. Can J Kidney Health Dis 2022; 9:20543581211069225

47. Li K, Hu Z, Li W, Shah K, Sessler D: Tight perioperative blood pressure management to reduce complications: A randomised feasibility trial. BMJ Open 2023; 13:e071328

48. Chiu C, Fong N, Lazzareschi D, et al.: Fluids, vasopressors, and acute kidney injury after major abdominal surgery between 2015 and 2019: A multicentre retrospective analysis. Br J Anaesth 2022; 129:317–26

49. Karkouti K, Wijeysundera DN, Yau TM, et al.: Acute kidney injury after cardiac surgery: Focus on modifiable risk factors. Circulation 2009; 119:495–502

50. Ripoll JG, Smith MM, Hanson AC, et al.: Sex-specific associations between preoperative anemia and postoperative clinical outcomes in patients undergoing cardiac surgery. Anesth Analg 2021; 132:1101–11

51. Padmanabhan H, Siau K, Curtis J, et al.: Preoperative anemia and outcomes in cardiovascular surgery: Systematic review and meta-analysis. Ann Thorac Surg 2019; 108:1840–8

52. Padmanabhan H, Siau K, Nevill AM, et al.: Intravenous iron does not effectively correct preoperative anaemia in cardiac surgery: A pilot randomized controlled trial. Interact Cardiovasc Thorac Surg 2019; 28:447–54

53. LaPar DJ, Hawkins RB, McMurry TL, et al.; Investigators for the Virginia Cardiac Services Quality Initiative: Preoperative anemia versus blood transfusion: Which is the culprit for worse outcomes in cardiac surgery? J Thorac Cardiovasc Surg 2018; 156:66–74.e2

54. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ: Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002; 74:1180–6

55. Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD: Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007; 116:2544–52

56. Vourc'h M, Roquilly A, Foucher A, et al.: Transfusion-related renal dysfunction after cardiac surgery: The role of myeloid-related protein_14 in neutrophil-mediated tubular damage. JACC Basic Transl Sci 2022; 7:627–38

57. Carson JL, Terrin ML, Noveck H, et al.; FOCUS Investigators: Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453–62

58. Hébert PC, Wells G, Blajchman MA, et al.: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340:409–17

59. Hajjar LA, Vincent J-L, Galas FRBG, et al.: Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. JAMA 2010; 304:1559–67

60. Mazer CD, Whitlock RP, Fergusson DA, et al.; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group: Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 2017; 377:2133–44

61. Carson JL, Stanworth SJ, Guyatt G, et al.: Red blood cell transfusion: 2023 AABB international guidelines. JAMA 2023; 330:1892–902

62. Guidet B, Soni N, Della Rocca G, et al.: A balanced view of balanced solutions. Crit Care 2010; 14:325

63. Orbegozo Cortés D, Rayo Bonor A, Vincent JL: Isotonic crystalloid solutions: A structured review of the literature. Br J Anaesth 2014; 112:968–81

64. Self WH, Semler MW, Wanderer JP, et al.; SALT-ED Investigators: Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med 2018; 378:819–28

65. Prough DS, Bidani A: Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999; 90:1247–9

66. Vignarajah M, Berg A, Abdallah Z, et al.: Intraoperative use of balanced crystalloids versus 0.9% saline: A systematic review and meta-analysis of randomised controlled studies. Br J Anaesth 2023; 131:463–71

67. Maheshwari K, Turan A, Makarova N, et al.: Saline versus lactated Ringer's solution: The Saline or Lactated Ringer's (SOLAR) trial. Anesthesiology 2020; 132:614–24

68. Hammond NE, Zampieri FG, Di Tanna GL, et al.: Balanced crystalloids versus saline in critically ill adults — A systematic review with meta-analysis. NEJM Evidence 2022; 1:EVIDoa2100010

69. Zampieri FG, Machado FR, Biondi RS, et al.; BaSICS Investigators and the BRICNet Members: Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: The BaSICS randomized clinical trial. JAMA 2021; 326:1–12

70. Semler MW, Self WH, Wanderer JP, et al.; SMART Investigators and the Pragmatic Critical Care Research Group: Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018; 378:829–39

71. Joosten A, Delaporte A, Mortier J, et al.: Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. Anesthesiology 2019; 130:227–36

72. Müller RB, Haase N, Lange T, Wetterslev J, Perner A: Acute kidney injury with hydroxyethyl starch 130/0.42 in severe sepsis. Acta Anaesthesiol Scand 2015; 59:329–36

73. Myburgh JA, Finfer S, Bellomo R, et al.; CHEST Investigators: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901–11

74. Perner A, Haase N, Guttormsen AB, et al.; 6S Trial Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367:124–34

75. Kancir ASP, Johansen JK, Ekeloef NP, Pedersen EB: The effect of 6% hydroxyethyl starch 130/0.4 on renal function, arterial blood pressure, and vasoactive hormones during radical prostatectomy: A randomized controlled trial. Anesth Analg 2015; 120:608–18

76. Pagel J-I, Rehm M, Kammerer T, et al.: Hydroxyethyl starch 130/0.4 and its impact on perioperative outcome: A propensity score matched controlled observation study. Anesth Analg 2018; 126:1949–56

77. Haase N, Perner A, Hennings LI, et al.: Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: Systematic review with meta-analysis and trial sequential analysis. BMJ 2013; 346:f839

78. Roberts I, Shakur H, Bellomo R, et al.: Hydroxyethyl starch solutions and patient harm. Lancet 2018; 391:736

79. Zarychanski R, Abou-Setta AM, Turgeon AF, et al.: Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: A systematic review and meta-analysis. JAMA 2013; 309:678–88

80. Podgoreanu MV, Mamoun N: Albumin vs crystalloid fluid for resuscitation in cardiac surgery: New evidence and arguments in the timeless debate. JAMA 2022; 328:246–8

81. Skubas NJ, Callum J, Bathla A, et al.; International Collaboration for Transfusion Medicine Guidelines: Intravenous albumin in cardiac and vascular surgery: A systematic review and meta-analysis. Br J Anaesth 2024; 132:237–50

82. Pesonen E, Vlasov H, Suojaranta R, et al.: Effect of 4% albumin solution vs Ringer acetate on major adverse events in patients undergoing cardiac surgery with cardiopulmonary bypass: A randomized clinical trial. JAMA 2022; 328:251–8

83. Onuoha OC, Arkoosh VA, Fleisher LA: Choosing wisely in anesthesiology: The gap between evidence and practice. JAMA Intern Med 2014; 174:1391–5

84. Mattos AZ, Schacher FC, Mattos AA: Vasoconstrictors in hepatorenal syndrome - A critical review. Ann Hepatol 2019; 18:287–90

85. Singh V, Ghosh S, Singh B, et al.: Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: A randomized study. J Hepatol 2012; 56:1293–8

86. Israelsen M, Krag A, Allegretti AS, et al.: Terlipressin versus other vasoactive drugs for hepatorenal syndrome. Cochrane Database Syst Rev 2017; 9:CD011532

87. Batool S, Waheed MD, Vuthaluru K, et al.: Efficacy of intravenous albumin for spontaneous bacterial peritonitis infection among patients with cirrhosis: A meta-analysis of randomized control trials. Cureus 2022; 14:e33124

88. Narula N, Tsoi K, Marshall JK: Should albumin be used in all patients with spontaneous bacterial peritonitis? Can J Gastroenterol 2011; 25:373–6

89. Arora V, Vijayaraghavan R, Maiwall R, et al.: Paracentesis-induced circulatory dysfunction with modest-volume paracentesis is partly ameliorated by albumin infusion in acute-on-chronic liver failure. Hepatology 2020; 72:1043–55

90. Ginès P, Titó L, Arroyo V, et al.: Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988; 94:1493–502

91. Aithal GP, Palaniyappan N, China L, et al.: Guidelines on the management of ascites in cirrhosis. Gut 2021; 70:9–29

92. Ostermann M, Liu K, Kashani K: Fluid management in acute kidney injury. Chest 2019; 156:594–603

93. Wang N, Jiang L, Zhu B, Wen Y Xi X-M; The Beijing Acute Kidney Injury Trial (BAKIT) Workgroup: Fluid balance and mortality in critically ill patients with acute kidney injury: A multicenter prospective epidemiological study. Crit Care 2015; 19:1–11

94. Ostermann M, Straaten HMO, Forni LG: Fluid overload and acute kidney injury: Cause or consequence? Crit Care 2015; 19:443

95. Myles PS, Bellomo R, Corcoran T, et al.; Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med 2018; 378:2263–74

96. Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE: Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: A randomized clinical trial. Anesthesiology 2014; 120:365–77

97. Marik PE, Cavallazzi R: Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. Crit Care Med 2013; 41:1774–81

98. Jacquet-Lagrèze M, Berthod C, Schweizer R, et al.: Venous congestion is more accurate than hypotension in predicting acute kidney injury after cardiac surgery. Comment on Br J Anaesth 2021; 126: 599-607. Br J Anaesth 2021; 127:e81–2

99. Mendez CE, Der Mesropian PJ, Mathew RO, Slawski B: Hyperglycemia and acute kidney injury during the perioperative period. Curr Diab Rep 2016; 16:10

100. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. Ann Intern Med 1998; 128:194–203

101. Palomba H, Castro I de, Neto ALC, Lage S, Yu L: Acute kidney injury prediction following elective cardiac surgery: AKICS score. Kidney Int 2007; 72:624–31

102. Schetz M, Vanhorebeek I, Wouters PJ, Wilmer A, Van den Berghe G: Tight blood glucose control is renoprotective in critically ill patients. J Am Soc Nephrol 2008; 19:571–8

103. Van den Berghe G, Wilmer A, Milants I, et al.: Intensive insulin therapy in mixed medical/surgical intensive care units: Benefit versus harm. Diabetes 2006; 55:3151–9

104. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004; 79:992–1000

105. Gandhi GY, Nuttall GA, Abel MD, et al.: Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: A randomized trial. Ann Intern Med 2007; 146:233–43

106. Finfer S, Chittock DR, et al.; NICE-SUGAR Study Investigators: Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283–97

107. Liu X, Hu Q, Chen Q, Jia J, Liao Y-H, Feng J: Effect of dexmedetomidine for prevention of acute kidney injury after cardiac surgery: An updated systematic review and meta-analysis. Ren Fail 2022; 44:1150–9

108. Hong E, Alfadhel A, Ortoleva J: Perioperative dexmedetomidine and renal protection: Promising and more investigation is warranted. J Cardiothorac Vasc Anesth 2022; 36:3725–6

109. STARSurg Collaborative: Association between peri-operative angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers and acute kidney injury in major elective non-cardiac surgery: A multicentre, prospective cohort study. Anaesthesia 2018; 73:1214–22

110. Fleisher LA, Fleischmann KE, Auerbach AD, et al.; American College of Cardiology: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014; 64:e77–137

111. Vassallo MC, Tartamella F, Testa F: To stop or not? Withholding anti-hypertensive therapy before surgery is not safe. J Cardiothorac Vasc Anesth 2017; 31:e92–3

112. Roshanov P, Rochwerg B, Patel A, et al.: Withholding versus continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: An analysis of the Vascular events In noncardiac Surgery patIents cOhort evaluatioN prospective cohort. Anesthesiology 2017; 126:16–27

113. Zou Z, Yuan HB, Yang B, et al.: Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults. Cochrane Database Syst Rev 2016; 2017:CD009210

114. Coca SG, Garg AX, Swaminathan M, et al.; TRIBE-AKI Consortium: Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrol Dial Transplant 2013; 28:2787–99

115. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N: Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: A systematic review. Br J Anaesth 2011; 106:292–7

116. Bell S, Rennie T, Marwick CA, Davey P: Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. Cochrane Database Syst Rev 2018; 11:CD011274

117. Barreto EF, Rule AD: Management of drug-associated acute interstitial nephritis. Kidney360 2020; 1:62–4

118. MHRA Regulating Medicine and Medical Devices. Drug Safety Update. Available at: https://webarchive.nationalarchives.gov.uk/ukgwa/20141206024920/https://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON046451. Accessed January 7, 2024.

119. McIlroy DR, Feng X, Shotwell M, et al.: Candidate kidney protective strategies for patients undergoing major abdominal surgery: A secondary analysis of the RELIEF trial cohort. Anesthesiology 2024; 140:1111–25

120. Parikh SV, Madhavan S, Shapiro J, et al.; Kidney Precision Medicine Project: Characterization of glomerular and tubulointerstitial proteomes in a case of nonsteroidal anti-inflammatory drug–attributed acute kidney injury: A clinical pathologic molecular correlation. Clin J Am Soc Nephrol 2023; 18:402–10

121. Goldstein SL, Mottes T, Simpson K, et al.: A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney Int 2016; 90:212–21

122. Morales-Alvarez MC: Nephrotoxicity of antimicrobials and antibiotics. Adv Chronic Kidney Dis 2020; 27:31–7

123. Rao QA, Newhouse JH: Risk of nephropathy after intravenous administration of contrast material: A critical literature analysis. Radiology 2006; 239:392–7

124. Davenport MS, Perazella MA, Yee J, et al.: Use of intravenous iodinated contrast media in patients with kidney disease: Consensus statements from the American College of Radiology and the National Kidney Foundation. Kidney Med 2020; 2:85–93

125. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH: Contrast material–induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: Risk stratification by using estimated glomerular filtration rate. Radiology 2013; 268:719–28

126. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE: Risk of intravenous contrast material–mediated acute kidney injury: A propensity score–matched study stratified by baseline-estimated glomerular filtration rate. Radiology 2014; 271:65–73

127. Dekkers IA, van der Molen AJ: Propensity score matching as a substitute for randomized controlled trials on acute kidney injury after contrast media administration: A systematic review. AJR Am J Roentgenol 2018; 211:822–6

128. James JH, Davenport MS, Dillman JR: American College of Radiology Manual on Contrast Media Version 10.1. ACR Committee on Drugs and Contrast. Available at: https://www.acr.org/-/media/acr/files/clinical-resources/contrast_media.pdf. Accessed March 20, 2024.

129. Pistolesi V, Regolisti G, Morabito S, et al.: Contrast medium induced acute kidney injury: A narrative review. J Nephrol 2018; 31:797–812

130. Karlsberg RP, Dohad SY, Sheng R; Iodixanol Peripheral Computed Tomographic Angiography Study Investigator Panel: Contrast medium–induced acute kidney injury: Comparison of intravenous and intraarterial administration of iodinated contrast medium. J Vasc Interv Radiol 2011; 22:1159–65

131. Laskey WK, Jenkins C, Selzer F, et al.; NHLBI Dynamic Registry Investigators: Volume-to-creatinine clearance ratio: A pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. J Am Coll Cardiol 2007; 50:584–90

132. Meersch M, Schmidt C, Hoffmeier A, et al.: Erratum to: Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. Intensive Care Med 2017; 43:1749

133. Shen W, Wu Z, Wang Y, Sun Y, Wu A: Impact of Enhanced Recovery After Surgery (ERAS) protocol versus standard of care on postoperative acute kidney injury (AKI): A meta-analysis. PLoS One 2021; 16:e0251476

134. Ostermann M, Cennamo A, Meersch M, Kunst G: A narrative review of the impact of surgery and anaesthesia on acute kidney injury. Anaesthesia 2020; 75(suppl 1):e121–33

135. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group: Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (part 1). Crit Care 2013; 17:204

136. Meersch M, Schmidt C, Hoffmeier A, et al.: Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. Intensive Care Med 2017; 43:1551–61

137. Göcze I, Jauch D, Götz M, et al.: Biomarker-guided intervention to prevent acute kidney injury after major surgery: The prospective randomized BigpAK study. Ann Surg 2018; 267:1013–20

138. Ransley DG, See EJ, Mizrahi A, Robbins R, Bellomo R: Inpatient and outpatient nephrology management of critically ill patients with acute kidney injury. Nephrology (Carlton) 2021; 26:319–27

139. Smith G, Nielsen M: Criteria for admission. BMJ 1999; 318:1544–7

140. Chawla LS, Davison DL, Brasha-Mitchell E, et al.: Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Crit Care 2013; 17:R207

141. Patschan D, Patschan S, Buschmann I, Ritter O: Loop diuretics in acute kidney injury prevention, therapy, and risk stratification. Kidney Blood Press Res 2019; 44:457–64

142. Bove T, Belletti A, Putzu A, et al.: Intermittent furosemide administration in patients with or at risk for acute kidney injury: Meta-analysis of randomized trials. PLoS One 2018; 13:e0196088

143. Shah R, Wood SJ, Khan SA, Chaudhry A, Rehan Khan M, Morsy MS: High-volume forced diuresis with matched hydration using the RenalGuard System to prevent contrast-induced nephropathy: A meta-analysis of randomized trials. Clin Cardiol 2017; 40:1242–6

144. Occhipinti G, Laudani C, Spagnolo M, Greco A, Capodanno D: Diuresis-matched versus standard hydration in patients undergoing percutaneous cardiovascular procedures: Meta-analysis of randomized clinical trials. Rev Esp Cardiol (Engl Ed) 2023; 76:759–66

145. Moroni F, Baldetti L, Kabali C, et al.: Tailored versus standard hydration to prevent acute kidney injury after percutaneous coronary intervention: Network meta-analysis. J Am Heart Assoc 2021; 10:e021342

146. Gerrah R, Izhar U: Beneficial effect of aspirin on renal function post-cardiopulmonary bypass. Asian Cardiovasc Thorac Ann 2003; 11:304–8

147. Kulka PJ, Tryba M, Zenz M: Preoperative alpha sub 2-adrenergic receptor agonists prevent the

deterioration of renal function after cardiac surgery: Results of a randomized, controlled trial. Crit Care Med 1996; 24:947–52

148. Dieleman JM, Nierich AP, Rosseel PM, et al.; Dexamethasone for Cardiac Surgery (DECS) Study Group: Intraoperative high-dose dexamethasone for cardiac surgery: A randomized controlled trial. JAMA 2012; 308:1761–7

149. Garg AX, Chan MTV, Cuerden MS, et al.; SIRS Investigators: Effect of methylprednisolone on acute kidney injury in patients undergoing cardiac surgery with a cardiopulmonary bypass pump: A randomized controlled trial. CMAJ 2019; 191:E247–56

150. Ho KM, Morgan DJR: Meta-analysis of N-acetylcysteine to prevent acute renal failure after major surgery. Am J Kidney Dis 2009; 53:33–40

151. Wald R, Bagshaw SM; STARRT-AKI Investigators: Timing of initiation of renal-replacement therapy in acute kidney injury. Reply 2020; 383:1797–8

152. Bouchard J, Mehta RL: Timing of kidney support therapy in acute kidney injury: What are we waiting for? Am J Kidney Dis 2022; 79:417–26

153. Ostermann M, Bagshaw SM, Lumlertgul N, Wald R: Indications for and timing of initiation of KRT. Clin J Am Soc Nephrol 2023; 18:113–20

154. Vandenberghe W, Gevaert S, Kellum JA, et al.: Acute kidney injury in cardiorenal syndrome type 1 patients: A systematic review and meta-analysis. Cardiorenal Med 2016; 6:116–28

155. Cheruku SR, Raphael J, Neyra JA, Fox AA: Acute kidney injury after cardiac surgery: Prediction, prevention, and management. ANESTHESIOLOGY 2023; 139:880–98

156. Mehta RH, Grab JD, O'Brien SM, et al.; Society of Thoracic Surgeons National Cardiac Surgery Database Investigators: Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. Circulation 2006; 114:2208–16; quiz 2208

157. Wijeysundera DN, Karkouti K, Dupuis J-Y, et al.: Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. JAMA 2007; 297:1801–9

158. Del Duca D, Iqbal S, Rahme E, Goldberg P, de Varennes B: Renal failure after cardiac surgery: Timing of cardiac catheterization and other perioperative risk factors. Ann Thorac Surg 2007; 84:1264–71

159. Molnar AO, Parikh CR, Sint K, et al.: Association of postoperative proteinuria with AKI after cardiac surgery among patients at high risk. Clin J Am Soc Nephrol 2012; 7:1749–60

160. Kristovic D, Horvatic I, Husedzinovic I, et al.: Cardiac surgery-associated acute kidney injury: Risk factors analysis and comparison of prediction models. Interact Cardiovasc Thorac Surg 2015; 21:366–73

161. Peng K, McIlroy DR, Bollen BA, et al.: Society of Cardiovascular Anesthesiologists clinical practice update for management of acute kidney injury associated with cardiac surgery. Anesth Analg 2022; 135:744–56

162. Ranucci M, Johnson I, Willcox T, et al.: Goal-directed perfusion to reduce acute kidney injury: A randomized trial. J Thorac Cardiovasc Surg 2018; 156:1918–27.e2

163. Mukaida H, Matsushita S, Yamamoto T, et al.: Oxygen delivery-guided perfusion for the prevention of acute kidney injury: A randomized controlled trial. J Thorac Cardiovasc Surg 2023; 165:750–60.e5

164. Guinn NR, Schwartz J, Arora RC, et al.: Perioperative Quality Initiative and Enhanced Recovery After Surgery-Cardiac Society consensus statement on the management of preoperative anemia and iron deficiency in adult cardiac surgery patients. Anesth Analg 2022; 135:532–44

165. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al.: Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: The VANCS randomized controlled trial. ANESTHESIOLOGY 2017; 126:85–93

166. Zarbock A, Küllmar M, Ostermann M, et al.: Prevention of cardiac surgery-associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: The PrevAKI-Multicenter Randomized Controlled Trial. Anesth Analg 2021; 133:292–302

167. STS Adult Cardiac Surgery Database specifications. Available at: https://www.sts.org/sites/default/files/documents/ACSD_DataSpecificationsV2_81.pdf. Accessed October 16, 2024.

168. Machado MN, Nakazone MA, Maia LN: Prognostic value of acute kidney injury after cardiac surgery according to kidney disease: Improving Global Outcomes Definition and Staging (KDIGO) criteria. PLoS One 2014; 9:e98028

169. Katabi LJ, Pu X, Yilmaz HO, Jia Y, Leung S, Duncan AE: Prognostic utility of KDIGO urine output criteria after cardiac surgery. J Cardiothorac Vasc Anesth 2021; 35:2991–3000

170. Howitt SH, Grant SW, Caiado C, et al.: The KDIGO acute kidney injury guidelines for cardiac surgery patients in critical care: A validation study. BMC Nephrol 2018; 19:149

171. Angeli P, Ginès P, Wong F, et al.: Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. J Hepatol 2015; 62:968–74

172. Nadim MK, Kellum JA, Forni L, et al.: Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol 2024; 81:163–83

173. Wong F, O'Leary JG, Reddy KR, et al.; North American Consortium for Study of End-Stage Liver

Disease: New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. Gastroenterology 2013; 145:1280–8.e1

174. Damodaran S, Bullock B, Ekwenna O, et al.: Risk factors for delayed graft function and their impact on graft outcomes in live donor kidney transplantation. Int Urol Nephrol 2021; 53:439–46

175. Kim DW, Tsapepas D, King KL, et al.: Financial impact of delayed graft function in kidney transplantation. Clin Transplant 2020; 34:e14022

176. Troppmann C, Gillingham KJ, Benedetti E, et al.: Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. The multivariate analysis. Transplantation 1995; 59:962–8

177. Perico N, Cattaneo D, Sayegh MH, Remuzzi G: Delayed graft function in kidney transplantation. Lancet 2004; 364:1814–27

178. Yarlagadda SG, Coca SG, Formica RN Jr, Poggio ED, Parikh CR: Association between delayed graft function and allograft and patient survival: A systematic review and meta-analysis. Nephrol Dial Transplant 2009; 24:1039–47

179. Rosenthal JT, Danovitch GM, Wilkinson A, Ettenger RB: The high cost of delayed graft function in cadaveric renal transplantation. Transplantation 1991; 51:1115–8

180. Freedland SJ, Shoskes DA: Economic impact of delayed graft function and suboptimal kidneys. Transplant Rev 1999; 13:23–30

181. Irish WD, McCollum DA, Tesi RJ, et al.: Nomogram for predicting the likelihood of delayed graft function in adult cadaveric renal transplant recipients. J Am Soc Nephrol 2003; 14:2967–74

182. Redfield RR, Scalea JR, Zens TJ, et al.: Predictors and outcomes of delayed graft function after living-donor kidney transplantation. Transpl Int 2016; 29:81–7

183. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL: Delayed graft function: Risk factors and implications for renal allograft survival. Transplantation 1997; 63:968–74

184. Troppmann C, Ormond DB, Perez RV: Laparoscopic (vs. open) live donor nephrectomy: A UNOS database analysis of early graft function and survival. Am J Transplant 2003; 3:1295–301

185. Wen Y, Parikh CR: Current concepts and advances in biomarkers of acute kidney injury. Crit Rev Clin Lab Sci 2021; 58:354–68

186. Oh D-J: A long journey for acute kidney injury biomarkers. Ren Fail 2020; 42:154–65

187. Lo DJ, Kaplan B, Kirk AD: Biomarkers for kidney transplant rejection. Nat Rev Nephrol 2014; 10:215–25

188. Edelstein CL: Biomarkers of acute kidney injury. Adv Chronic Kidney Dis 2008; 15:222–34

189. Krawczeski CD, Goldstein SL, Woo JG, et al.: Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. J Am Coll Cardiol 2011; 58:2301–9

190. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P: Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol 2010; 5:395–401

191. Parikh CR, Butrymowicz I, Yu A, et al.; ASSESS-AKI Study Investigators: Urine stability studies for novel biomarkers of acute kidney injury. Am J Kidney Dis 2014; 63:567–72

192. Moledina DG, Wilson FP, Pober JS, et al.: Urine TNF-α and IL-9 for clinical diagnosis of acute interstitial nephritis. JCI Insight 2019; 4:127456

193. Mansour SG, Puthumana J, Coca SG, Gentry M, Parikh CR: Biomarkers for the detection of renal fibrosis and prediction of renal outcomes: A systematic review. BMC Nephrol 2017; 18:72

194. Zheng C-M, Liao M-T, Lin M-Y, et al.: Biomarkers in acute kidney injury. Open J Nephrol 2013; 03:51–60

195. Parikh CR, Coca SG, Thiessen-Philbrook H, et al.; TRIBE-AKI Consortium: Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 2011; 22:1748–57

196. Haase-Fielitz A, Haase M, Devarajan P: Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: A critical evaluation of current status. Ann Clin Biochem 2014; 51:335–51

197. Zhang B, Song Y, Ma Q, Yang J, Bai L: Expression and Significance of KIM-1, NGAL, and HO-1 in patients with acute kidney injury after cardiac valve replacement. J Inflamm Res 2023; 16:2755–61

198. McIlroy DR, Wagener G, Lee HT: Biomarkers of acute kidney injury: An evolving domain. Anesthesiology 2010; 112:998–1004

199. Schley G, Köberle C, Manuilova E, et al.: Comparison of plasma and urine biomarker performance in acute kidney injury. PLoS One 2015; 10:e0145042

200. Pan H-C, Yang S-Y, Chiou TT-Y, et al.: Comparative accuracy of biomarkers for the prediction of hospital-acquired acute kidney injury: A systematic review and meta-analysis. Crit Care 2022; 26:349

201. Endre ZH, Pickering JW, Walker RJ: Clearance and beyond: The complementary roles of GFR measurement and injury biomarkers in acute kidney injury (AKI). Am J Physiol Renal Physiol 2011; 301:F697–707

202. Zappitelli M, Bernier P-L, Saczkowski RS, et al.: A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. Kidney Int 2009; 76:885–92

203. Deng Y, Chi R, Chen S, et al.: Evaluation of clinically available renal biomarkers in critically ill

adults: A prospective multicenter observational study. Crit Care 2017; 21:46

204. Allinovi M, Sessa F, Villa G, et al.: Novel biomarkers for early detection of acute kidney injury and prediction of long-term kidney function decline after partial nephrectomy. Biomedicines 2023; 11:1046

205. Yong Z, Pei X, Zhu B, Yuan H, Zhao W: Predictive value of serum cystatin C for acute kidney injury in adults: A meta-analysis of prospective cohort trials. Sci Rep 2017; 7:41012

206. Han WK, Waikar SS, Johnson A, et al.: Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int 2008; 73:863–9

207. Amaral Pedroso L, Nobre V, Dias Carneiro de Almeida C, et al.: Acute kidney injury biomarkers in the critically ill. Clin Chim Acta 2020; 508:170–8

208. Morales-Buenrostro LE, Salas-Nolasco OI, Barrera-Chimal J, et al.: Hsp72 is a novel biomarker to predict acute kidney injury in critically ill patients. PLoS One 2014; 9:e109407

209. Devarajan P: Biomarkers for the early detection of acute kidney injury. Curr Opin Pediatr 2011; 23:194–200

210. Wilnes B, Castello-Branco B, Branco BC, Sanglard A, Vaz de Castro PAS, Simões-E-Silva AC: Urinary L-FABP as an early biomarker for pediatric acute kidney injury following cardiac surgery with cardiopulmonary bypass: A systematic review and meta-analysis. Int J Mol Sci 2024; 25:4912

211. Cummings JJ, Shaw AD, Shi J, Lopez MG, O'Neal JB, Billings FT: Intraoperative prediction of cardiac surgery–associated acute kidney injury using urinary biomarkers of cell cycle arrest. J Thorac Cardiovasc Surg 2019; 157:1545–53.e5

212. Antonelli A, Allinovi M, Cocci A, et al.; AGILE Group: The predictive role of biomarkers for the detection of acute kidney injury after partial or radical nephrectomy: A systematic review of the literature. Eur Urol Focus 2020; 6:344–53

213. Elmedany SM, Naga SS, Elsharkawy R, Mahrous RS, Elnaggar AI: Novel urinary biomarkers and the early detection of acute kidney injury after open cardiac surgeries. J Crit Care 2017; 40:171–7

214. Vanmassenhove J, Steen J, Vansteelandt S, et al.: The importance of the urinary output criterion for the detection and prognostic meaning of AKI. Sci Rep 2021; 11:11089

215. Coca SG, Nadkarni GN, Garg AX, et al.; TRIBE-AKI Consortium: First post-operative urinary kidney injury biomarkers and association with the duration of AKI in the TRIBE-AKI cohort. PLoS One 2016; 11:e0161098

216. Menez S, Ju W, Menon R, et al.; Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) Consortium and the Kidney Precision Medicine Project: Urinary EGF and MCP-1 and risk of CKD after cardiac surgery. JCI Insight 2021; 6:e147464

217. Rao VS, Ahmad T, Brisco-Bacik MA, et al.: Renal effects of intensive volume removal in heart failure patients with preexisting worsening renal function. Circ Heart Fail 2019; 12:e005552

218. Kidney Precision Medicine Project. Available at: https://www.niddk.nih.gov/research-funding/research-programs/kidney-precision-medicine-project-kpmp. Accessed January 5, 2024.

219. Khan A, Turchin MC, Patki A, et al.: Genome-wide polygenic score to predict chronic kidney disease across ancestries. Nat Med 2022; 28:1412–20

220. Larach DB, Engoren MC, Schmidt EM, Heung M: Genetic variants and acute kidney injury: A review of the literature. J Crit Care 2018; 44:203–11

221. Bhatraju PK, Stanaway IB, Palmer MR, et al.: Genome-wide association study for AKI. Kidney360 2023; 4:870–80

222. Larach DB, Lewis A, Bastarache L, et al.: Limited clinical utility for GWAS or polygenic risk score for postoperative acute kidney injury in non-cardiac surgery in European-ancestry patients. BMC Nephrol 2022; 23:339

223. Stafford-Smith M, Li Y-J, Mathew JP, et al.; Duke Perioperative Genetics and Safety Outcomes (PEGASUS) Investigative Team: Genome-wide association study of acute kidney injury after coronary bypass graft surgery identifies susceptibility loci. Kidney Int 2015; 88:823–32

224. Zhao B, Lu Q, Cheng Y, et al.; TRIBE-AKI Consortium: A genome-wide association study to identify single-nucleotide polymorphisms for acute kidney injury. Am J Respir Crit Care Med 2017; 195:482–90

225. Douville NJ, Larach DB, Lewis A, et al.: Genetic predisposition may not improve prediction of cardiac surgery-associated acute kidney injury. Front Genet 2023; 14:1094908

226. Westphal S, Gruenewald B: Genome-wide association study of myocardial infarction, atrial fibrillation, acute stroke, acute kidney injury and delirium after cardiac surgery–A sub-analysis of the RIPHeart-Study. BMC Cardiovasc Disord 2019; 19:26

227. Tallarico RT, McCoy IE, Dépret F, Legrand M: Meaning and management of perioperative oliguria. Anesthesiology 2024; 140:304–12

228. Meybohm P, Bein B, Brosteanu O, et al.; RIPHeart Study Collaborators: A multicenter trial of remote ischemic preconditioning for heart surgery. N Engl J Med 2015; 373:1397–407