ANESTHESIOLOGY

Perioperative Acute Kidney Injury

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ABSTRACT

Perioperative organ injury is among the leading causes of morbidity and mortality of surgical patients. Among different types of perioperative organ injury, acute kidney injury occurs particularly frequently and has an exceptionally detrimental effect on surgical outcomes. Currently, acute kidney injury is most commonly diagnosed by assessing increases in serum creatinine concentration or decreased urine output. Recently, novel biomarkers have become a focus of translational research for improving timely detection and prognosis for acute kidney injury. However, specificity and timing of biomarker release continue to present challenges to their integration into existing diagnostic regimens. Despite many clinical trials using various pharmacologic or nonpharmacologic interventions, reliable means to prevent or reverse acute kidney injury are still lacking. Nevertheless, several recent randomized multicenter trials provide new insights into renal replacement strategies, composition of intravenous fluid replacement, goal-directed fluid therapy, or remote ischemic preconditioning in their impact on perioperative acute kidney injury. This review provides an update on the latest progress toward the understanding of disease mechanism, diagnosis, and managing perioperative acute kidney injury, as well as highlights areas of ongoing research efforts for preventing and treating acute kidney injury in surgical patients.

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Over the past century, considerable progress has been made in anesthesia safety. Advancements in specialty training, improved monitoring modalities, and safer airway management have all contributed to better patient outcomes. However, surgical morbidity and mortality has essentially remained unchanged and continues to be a leading health burden in Western countries.[1] Among different types of organ injury, specifically with regard to organ dysfunction in the postoperative period, acute kidney injury remains particularly prominent, occurring in 20 to 40% of high-risk patients.[2] Moreover, patients with a diagnosis of sepsis and acute kidney injury have an associated mortality rate of 70%.[3] Current experimental outcomes suggest acute kidney injury may precipitate a decline in other organ systems, thus impacting rates of multiorgan failure, sepsis, and death.[4] Even subclinical acute kidney injury is correlated to an increased likelihood of mortality.[5] Preventing and treating acute kidney injury represents multiple obstacles toward improving outcomes among surgical patients.

Historically, treatment modalities toward prevention of acute kidney injury have been limited. For example, prophylactic use of low-dose dopamine ("renal dopamine") or treatment with high doses of furosemide to block adenosine triphosphate (ATP) consumption by renal tubular epithelial cells have proven detrimental instead of protective in perioperative clinical trials.[6] To make a definitive diagnosis early in the injury process and effectively treat perioperative acute kidney injury, the obstacle of finding reliable identification tools must be overcome. Approaches based on alterations of serum creatinine may delay identification and intervention because of its relatively late diagnostic presentation. Therefore, the search for novel and specific biomarkers toward early identification of acute kidney injury has challenged this field of research.

Based on these unresolved questions, mechanistic insight into acute kidney injury, novel biomarkers, and therapeutic modalities to prevent or treat are intense areas of research. Many ongoing translational studies and clinical trials are aiming to provide a more acute understanding of the disease process to establish diagnostic, preventive, or therapeutic options for acute kidney injury in perioperative patients. Through this review, we put these recent and ongoing studies into the context of established findings of perioperative acute kidney injury. We hope that these efforts will soon be successful and lead to an improvement in our diagnostic, preventive, or therapeutic options for surgical patients experiencing acute kidney injury.

Acute Kidney Injury Definition

Acute kidney injury is one of a number of acute kidney diseases occurring in the presence or absence of other acute or chronic renal disease processes.[7] A condition that affects kidney structure and function is categorized as acute or chronic,

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based upon interval of time. An inclusive nomenclature to enhance understanding and communication has been proposed to systematically classify functional and structural criteria for acute kidney injury, acute kidney disease, chronic kidney disease, and no known kidney disease (Supplementary Digital Content, http://links.lww.com/ALN/C55).[7]

The publication of Risk, Injury, Failure, Loss, End-stage renal disease criteria (RIFLE) in 2004 created a standard, widely used definition for acute kidney injury.[8] The establishment of these standards ended a plethora of over 35 definitions for acute kidney injury in acute renal failure literature.[9] These standardized criteria established a uniform manner to define acute kidney injury, improving accuracy in reporting incidence and outcomes and allowing comparability of studies regarding the diagnosis of acute kidney injury. This allowed our understanding to evolve from a "simple loss of function" to a more mature reality where acute kidney injury is a multifaceted, heterogeneous disease process.[10,11] However, a significant limitation of the Risk, Injury, Failure, Loss, End-stage renal disease standards is that it underestimated the effect of small acute creatinine changes on mortality as part of the criterion.[12] In response to this shortcoming, the Acute Kidney Injury Network (AKIN) modified the Risk, Injury, Failure, Loss, End-stage criteria, taking into account small increases in creatinine (at least 0.3 mg/dl) over time (at least 48 h) (table 1).[13] In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) task force offered a cohesive interpretation of the Risk, Injury, Failure, Loss, End-stage renal disease criteria, Acute Kidney Injury Network, and pediatric Risk, Injury, Failure, Loss, End-stage renal disease criteria (pRIFLE) as "a single definition for practice, research, and public health."[14] The Kidney Disease Improving Global Outcomes classification stages the presence of acute kidney injury from an acute increase in serum creatinine or a period of oliguria.[15] As it relates to time, the Acute Dialysis Quality Initiative Group recently clarified that "acute kidney injury" occurs within 48 h or less, and "acute kidney disease" occurs when acute kidney injury persists for 7 days or longer.[15]

Acute kidney injury has two subgroups, "subclinical acute kidney injury" and "functional acute kidney injury," and has recently been described with the introduction of biomarkers as a diagnostic tool.[16] Elevated concentrations of an acute kidney injury biomarker, without meeting Kidney Disease Improving Global Outcomes classifications, is defined as subclinical acute kidney injury, whereas functional acute kidney injury meets the Kidney Disease Improving Global Outcomes definition but fails to demonstrate an increase in biomarker concentration.[17] Although it is tempting to assume that subclinical acute kidney injury is an innocuous phenomenon with surgical patients, current evidence suggests that even minor increases of perioperative creatinine

Table 1. Acute Kidney Injury Classification Systems

RIFLE (7 days)	AKIN (48 h)	KDIGO
Risk Increased sCr × 1.5 or GFR decrease > 25% OR urine output < 0.5 ml · kg^{-1} · h^{-1} for 6 h	**Stage 1** Increased sCr × 1.5–2 or sCr increase ≥ 0.3 mg dl^{-1} OR urine output < 0.5 ml · kg^{-1} · h^{-1} for > 6 h	**Stage 1** Increased sCr × 1.5–1.9 within 7 days OR sCr increase ≥ 0.3 mg dl^{-1} within 48 h OR urine output < 0.5 ml · kg^{-1} · h^{-1} for 6–12 h
Injury Increased sCr × 2 or GFR decrease > 50% OR urine output < 0.5 ml · kg^{-1} · h^{-1} for 12 h	**Stage 2** Increased sCr × 2–3 OR urine output < 0.5 ml · kg^{-1} · h^{-1} for > 12h	**Stage 2** Increased sCr × 2–2.9 OR urine output < 0.5 ml · kg^{-1} · h^{-1} for ≥ 12 h
Failure Increased sCr × 3 or GFR decrease > 75% or sCr ≥ 4 mg dl^{-1} with an acute rise in sCr (≥ 0.5 mg dl^{-1}) OR urine output < 0.3 ml · kg^{-1} · h^{-1} for 24 h or anuria for 12 h	**Stage 3** Increased sCr × 3 or more or sCr ≥ 4 mg dl^{-1} with an acute rise in sCr (≥ 0.5 mg dl^{-1}) OR urine output < 0.3 ml · kg^{-1} · h^{-1} for > 24 h or anuria for 12 h	**Stage 3** Increased sCr × 3 or more or sCr ≥ 4 mg dl^{-1} or initiation of RRT or GFR decrease to < 35 ml min^{-1} (1.73 m)$^{-2}$ in patients < 18 yr old OR urine output < 0.3 ml · kg^{-1} · h^{-1} for ≥ 24 h or anuria for ≥ 12 h
Loss Persistent acute renal failure = complete loss of kidney function > 4 weeks		
End-stage renal disease End-stage kidney disease > 3 months		

Comparison of the three most notable and historic classification systems used to diagnose acute kidney injury. The initial system was the RIFLE (Risk, Injury, Failure, Loss of kidney function, End-stage renal failure), which was developed by an international consensus in 2004.[8] It defined five stages of renal injury: risk-end stage disease. A short time later, the Acute Kidney Injury Network (AKIN) developed its own diagnostic criteria that uses a smaller creatinine change to define acute kidney injury. This was based on studies showing that even small changes in serum creatinine resulted in adverse outcomes.[2–6] In 2012, the KDIGO (Kidney Disease: Improving Global Outcomes) classification system was produced and has been the main system in use since.[14]

GFR, glomerular filtration rate; sCr, serum creatinine.

levels—not meeting Kidney Disease Improving Global Outcomes definition for acute kidney injury—are related to a doubling of perioperative mortality and longer hospital length of stay.[5] Haase *et al.*[18] determined that even without diagnostic fluctuations in serum creatinine, subclinical acute kidney injury is associated with adverse outcomes.

Epidemiology of Perioperative Acute Kidney Injury

The effect of acute kidney injury on individual outcomes and healthcare systems is remarkable. Acute kidney injury in industrialized countries costs an estimated $1 billion, claims 300,000 lives, and contributes to the development of 300,000 advanced chronic kidney disease cases annually.[19,20] Acute kidney injury correlates with elevated mortality rates, longer hospital stays, and increased treatment expenses, with the seriousness of acute kidney injury directly linked to patient-centered outcomes. Although multiple studies have since substantiated the impact of acute kidney injury, the prevalence of acute kidney injury is dependent upon the definition, criteria, and study population.

Kork *et al.*[5] retrospectively examined 39,369 surgical patients in a single-center study utilizing the Kidney Disease Improving Global Outcomes criteria. Acute kidney injury occurred in 6% of the study population. After adjusting for multiple variables including age, hospital length of stay, sex, preoperative creatinine, and hemoglobin, the authors determined that minor changes in creatinine levels (25 to 49% above baseline) increased the risk of death by twofold and increased the length of hospitalization by 2 days.[5] In 2017, O'Connor *et al.*[21] investigated the association between postoperative acute kidney injury using the Kidney Disease Improving Global Outcomes standards for a retrospective cohort study and found that 6.8% of investigated patients sustained acute kidney injury resulting in a 13.3% in-hospital mortality rate compared with 0.9% without acute kidney injury ($P < 0.001$). At 1 year, 26.6% of patients with acute kidney injury died compared with 6.1% of patients without acute kidney injury ($P < 0.001$), resulting in an adjusted hazard ratio for death of 2.96 (95% CI, 1.86 to 4.71; $P < 0.001$) for acute kidney injury.[21] Both studies concluded that in noncardiac surgery patients, the presence of even mild forms of acute kidney injury posed a significant risk of death and increased the length of hospital stay.[5,21] The frequency, risk factors, and outcomes after noncardiac surgery have not been well identified and could offer a multitude of possibilities for further analysis in postoperative acute kidney injury research.

Cardiac surgery–associated acute kidney injury is a frequent source of perioperative acute kidney injury. Recent meta-analysis found the incidence of acute kidney injury in cardiac surgery patients to be as significant as 25 to 30%.[22,23] In 2016, Hu *et al.*[22] analyzed the pooled incidence rates of acute kidney injury in 300,000 postcardiac surgery patients and determined the incidence to be 22.3% (95% CI, 19.8 to 25.1). Utilizing Kidney Disease Improving Global Outcomes criteria, pooled rates for the development were 13.6, 3.8, and 2.7% for stages 1, 2, and 3, respectively, with 2.3% requiring renal replacement therapy.[22] The development of acute kidney injury increased the monetary cost and length of hospitalization.[22] The connection between acute kidney injury and postcardiac surgery has pronounced short- and long-term morbidity outcomes. In a cohort study looking at more than 1,000 patients undertaking elective cardiac surgery, acute kidney injury patients had a 26% 5-year cumulative risk of death, more than double the cumulative risk in patients without acute kidney injury.[24] Although the role of acute kidney injury is well established in patients receiving cardiac surgery, less information is available regarding noncardiac surgery.

To determine whether the type of surgery influenced whether a patient develops acute kidney injury, Grams *et al.*[25] performed a retrospective study of 161,185 Veterans Health Administration patients in 2016. Cardiac surgery presented the greatest risk for postoperative acute kidney injury (relative risk, 1.22; 95% CI, 1.17 to 1.27), proceeded by general thoracic (relative risk, 0.92; 95% CI, 0.87 to 0.98), orthopedic (relative risk, 0.70; 95% CI, 0.67 to 0.73), vascular (relative risk, 0.68; 95% CI, 0.64 to 0.71), urologic (relative risk, 0.65; 95% CI, 0.61 to 0.69), and ear, nose, and throat (relative risk, 0.32; 95% CI, 0.28 to 0.37).[25] Although cardiac surgery posed the greatest postoperative risk, similar risk factors including advanced age, African American race, hypertension, diabetes mellitus, and a lower estimated glomerular filtration rate was observed across surgical types.[25] Further, acute kidney injury postoperative patients had longer hospitalization, higher rates of 30-day readmission, heightened risk for developing end-stage renal disease, and higher mortality rates (19% *vs.* 8%). These findings corroborated research from Kork *et al.*[5] and O'Connor *et al.*[21] that examined the occurrence of morbidity with acute kidney injury among the noncardiac perioperative population. Taken together, these data indicate that the acute kidney injury occurs more frequently than previously anticipated. Even smaller changes in kidney function are associated with higher degrees of morbidity and mortality. Therefore, clinicians should carefully consider clinical and laboratory signs of mild kidney injury to be prepared to manage potential clinical complications, such as organ injury, multiorgan failure, or sepsis.

Pathophysiology of Perioperative Acute Kidney Injury

Historically, acute kidney injury was categorized into prerenal, renal, and postrenal causes. Prerenal acute kidney injury is a functional response to renal hypoperfusion, where intrinsic renal tubular function remains intact. Prerenal acute kidney injury results from a hypovolemic or low circulating volume or low cardiac output state. Postrenal acute kidney injury is caused by the blockage of urinary flow downstream in the urinary tract, inducing a backup into the kidney and consequent hydronephrosis. Like prerenal acute kidney injury, there is no inherent renal disease present if

urinary flow is reestablished before permanent structural damage develops. In contrast, intrinsic acute kidney injury results from a disease process of the renal vascular, glomeruli, tubules, or interstitium.[26] This traditional classification provides a convenient but somewhat simplistic framework, because acute kidney injury often crosses these boundaries. For example, prolonged prerenal acute kidney injury can lead to secondary intrinsic acute tubular necrosis.[27]

Perioperative acute kidney injury and the ways in which it develops is multifaceted and complex. Hypoperfusion, inflammation, and neuroendocrine response to surgery are the frequent mechanisms affecting renal perfusion.[28,29] Reduction of blood pressure and renal hypoperfusion are frequent consequences of perioperative hypovolemia, as well as the vasodilatory and cardiodepressant effects of anesthesia. In a low-perfusion state, the kidneys can exhibit remarkable autoregulation, maintaining constant renal blood flow and consequently glomerular filtration rate despite fluctuating mean arterial pressure and volume status. Prostaglandin signaling decreases afferent arteriolar resistance, which increases blood flow to the glomeruli and sustains the glomerular capillary pressure in a low-perfusion state. The activation of the renin–angiotensin–aldosterone systems and release of angiotensin II raises efferent arteriolar resistance, sustaining the glomerular capillary pressure.[26] If renal hypoperfusion persists or drops below the autoregulatory range, endogenous vasoconstrictors released from the renal sympathetic system result in afferent arteriolar vasoconstriction. This effectively reduces renal blood flow leading to renal tubular ischemia and reduced glomerular filtration rate.[26,30–32] The diminishing of oxygen balance induces renal tissue hypoxia and ATP starvation that stimulates extracellular matrix production, collagen deposition, and fibrosis.[33] As a metabolic product of ATP,[34] adenosine binds to kidney cell surface receptors to match blood flow with energy consumption.[2,35] The interstitial concentration of adenosine rises when neighboring cells are in a negative energy balance.[35] To recover from a negative energy balance and high oxygen demand, it is unnecessary to increase blood flow, but rather to lower the glomerular filtration fraction. This phenomenon has been termed "acute renal success."[36,37] By reducing the filtration rate, the number of sodium ions that must be transported per oxygen delivered is reduced, conserving energy and improving the energy balance.[35] Renal perfusion is capitalized to a rate that is adequate to promote healing while maintaining excretory function without the risk of inhibiting volume conservation.[36]

Renal autoregulation can also be disrupted by using nonsteroidal antiinflammatory drugs during the perioperative period. These inhibit the enzyme cyclooxygenase and prohibit the production of renal prostaglandins. This leads to the unopposed constriction of both the afferent and efferent arterioles by angiotensin II in a state of persistent renal hypoperfusion, decreasing renal perfusion flow and glomerular filtration rate (fig. 1).

In addition to hypoperfusion-induced injury, systemic inflammation and cytokine release caused by trauma and surgical stress directly induce tubular injury and subsequent systemic inflammation.[2,34,38] The etiology of this inflammation-induced acute kidney injury is multifactorial, including renin–angiotensin–aldosterone system activation, renal microcirculatory dysfunction, increased oxidative stress, cytokine-induced injury, endothelial cell injury, and activation of proapoptotic pathways.[27–29,39,40] All these factors predispose the surgical patient to develop acute kidney injury during the perioperative period. In recent years, evidence in both basic science and clinical research has led to a new understanding that acute kidney injury is not a mere singular organ injury. Acute kidney injury is now perceived as a multifaceted systemic disease process that engenders distant organ dysfunctions, including pulmonary,[41] cardiac,[42] neurologic, immunologic, hepatic, and gastrointestinal dysfunctions (fig. 2).[43–45] Recent studies highlight that acute kidney injury can cause remote organ injury, for example, to the intestine. Lee *et al.*[46] provide mechanistic insight of the inflammatory activation of Paneth cells that are contained at the bottom of crypts located at the intestinal mucosa. Activation of Paneth cells leads to massive release of inflammatory mediators (such as interleukin-17A), causing a disruption of the intestinal barrier function and translocation of bacteria from the intestinal lumen into the blood stream, promoting sepsis and multiorgan failure (fig. 3).[6] These studies highlight in an elegant way a functional role of acute kidney injury beyond its filter function, suggesting that kidney injury and acute kidney injury trigger inflammation and morbidity in distal organ systems.[4]

Many questions regarding organ "cross-talk" during acute kidney injury still remain unclear, for example how communication between the kidneys and distal organs—such as the gut, lungs, heart, or the brain—are communicated. Similarly, many mechanistic aspects of acute kidney injury continue to be the focus of basic and translational research. Experimental data suggest that during acute kidney injury, a combination of proinflammatory cytokine and chemokine release, leukocyte extravasation, induction of remote oxidative stress, and ion channels dysregulation can occur.[39,47] Similarly, a number of antiinflammatory pathways that can be targeted for acute kidney injury prevention or treatment have been identified, such as purinergic[48–50] or hypoxia-elicited antiinflammatory signaling pathways[51] or inflammatory endpoints that are under the control of microRNAs.[41,52–54]

Patient-associated Risk Factors for Acute Kidney Injury

Several elements are correlated with a heightened risk for perioperative acute kidney injury in patients. Preexisting perioperative elevation of creatinine (more than 1.2 mg/dl) is a significant predictor for postoperative acute kidney injury among both cardiac and noncardiac surgery

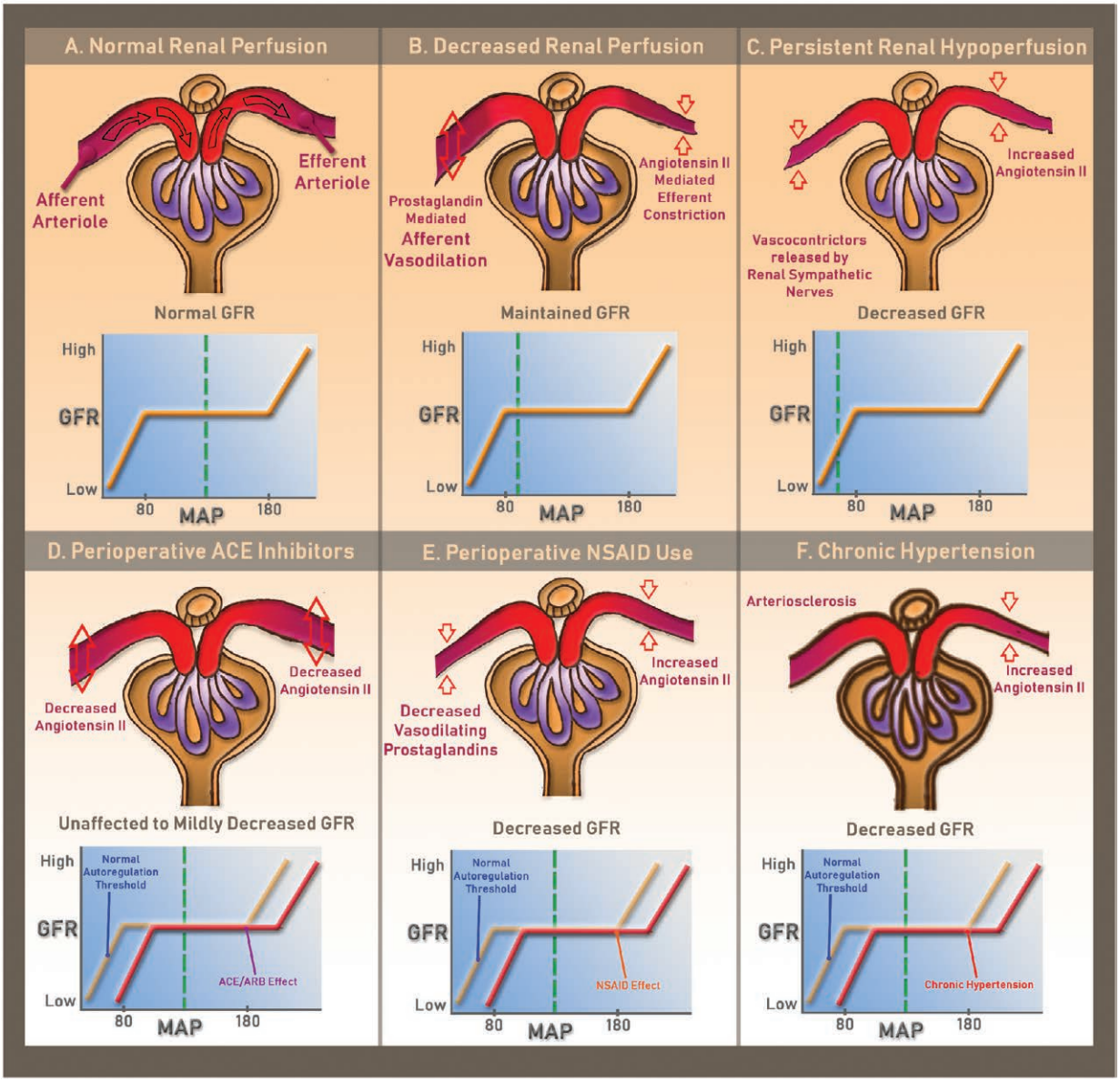

Fig. 1. Glomerular filtration as a function of glomerular blood flow. (*A*) Normal glomerular blood flow with normal glomerular filtration rate (GFR). (*B*) Reduced renal perfusion pressure within the autoregulatory range, caused by intraoperative conditions such as anesthesia and medication induced hypotension or hypovolemia. Normal GFR is maintained with prostaglandin-mediated afferent arteriolar vasodilation and angiotensin II–mediated efferent arteriolar vasoconstriction. (*C*) Persistent reduction in renal perfusion pressure below the autoregulatory range. This can be seen intraoperatively with protracted systemic hypotension or severe hypovolemia caused by hemorrhage and blood loss. In this state, endogenous vasoconstrictors released from the renal sympathetic nerves increase the afferent arteriolar resistance, which results in a rapid decline in GFR and a decrease in renal blood flow. This eventually leads to tubular cell damage and cell death. (*D*) Effect of angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB). Loss of angiotensin II decreases both the afferent and efferent arteriolar resistance, relaxing the efferent arteriole significantly more. The net clinical effect is unchanged or slightly decreased GFR. (*E*) Reduced GFR with nonsteroidal antiinflammatory drug (NSAID) use because of loss of vasodilatory prostaglandin. (*F*) Effect of chronic hypertension on the preglomerular arterial vessels, primarily the afferent arterioles. Chronic hypertension eventually leads to thickening of arteriole walls and narrowing of lumen, a process known as arteriolosclerosis. This results in inadequate blood flow through the glomeruli and may produce glomerular and tubulointerstitial ischemia. Conditions displayed in *D–F* can contribute to the development of "normotensive" perioperative acute kidney injury. MAP, mean arterial pressure.

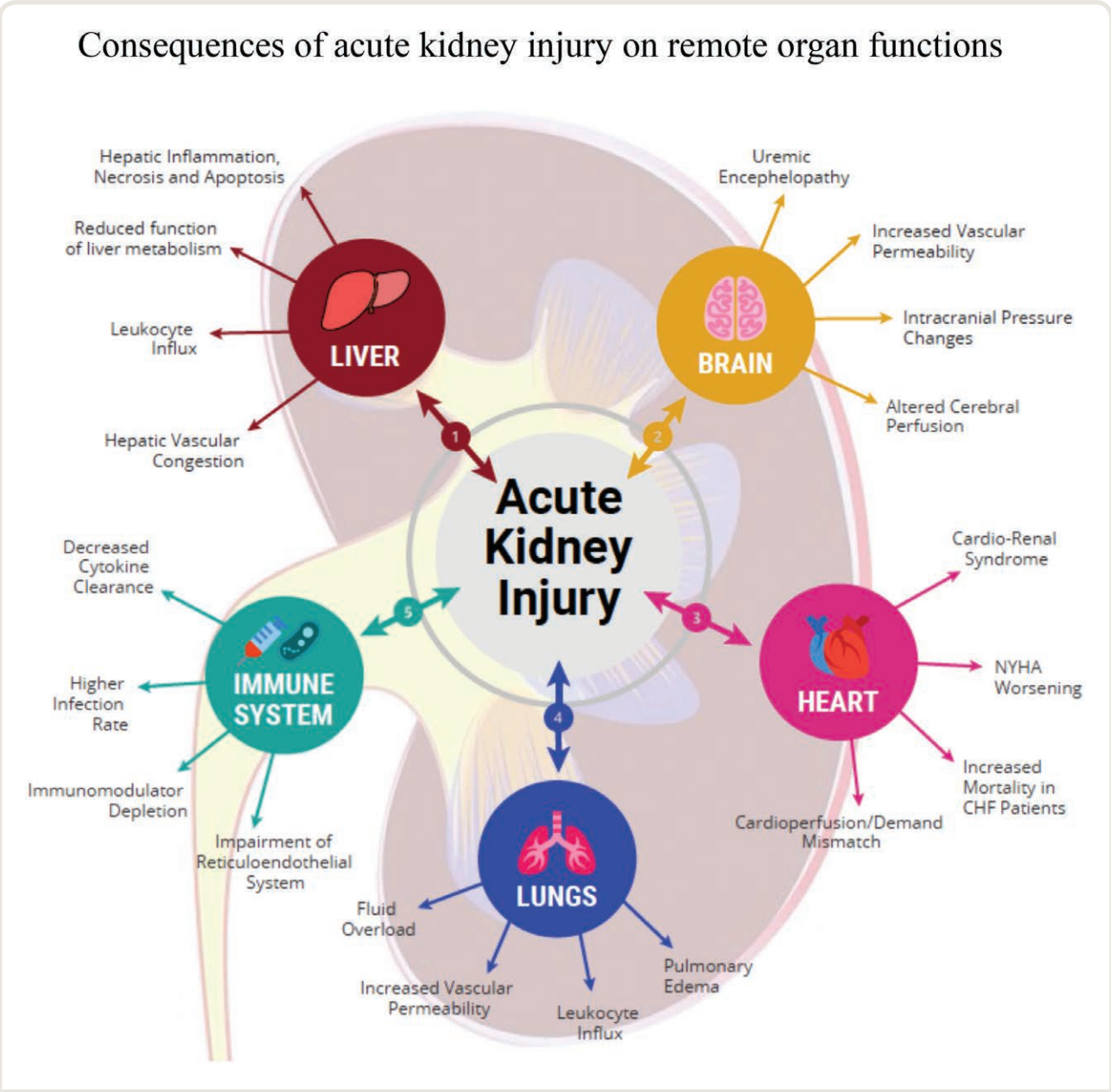

Fig. 2. Consequences of acute kidney injury on remote organ functions. There is increasing evidence that acute kidney injury directly contributes to remote injury in the heart, lung, brain, liver, immunologic, and other organ systems. In the hepatic system, acute kidney injury causes intestinal barrier breakdown and greater gut translocation and delivery of endotoxins and microorganisms to the portal system. This results in hepatic inflammation and apoptosis along with hepatic overproduction and systemic release of proinflammatory cytokines. Acute kidney injury is also associated with cerebral dysfunction, including uremic encephalopathy. Activation of neuroinflammatory cascade results in increase in vascular permeability and breakdown of blood–brain barrier. In the cardiac system, acute kidney injury is associated with cardiorenal syndrome, which is a state of concomitant heart and kidney failure. Suggested mechanisms of acute kidney injury–induced cardiac dysfunction include fluid overload and uremia-induced decrease in myocardial contractility. In the pulmonary system, the remote effect of acute kidney injury is due to activation of inflammatory cascade leading to an increase in pulmonary vascular permeability and lung neutrophil infiltration. This leads to accumulation of fluid within the lung tissue, causing pulmonary edema. In the immunologic system, acute kidney injury has a profound impact on humoral and cellular immunity and overall immunocompetence. This is due to a combination of increase in oxidative stress, impaired clearance of the reticuloendothelial system, and decreased clearance of circulating cytokines, leading to higher rate of infections in patients with acute kidney injury. CHF, congestive heart failure; NYHA, New York Heart Association classification of heart failure.

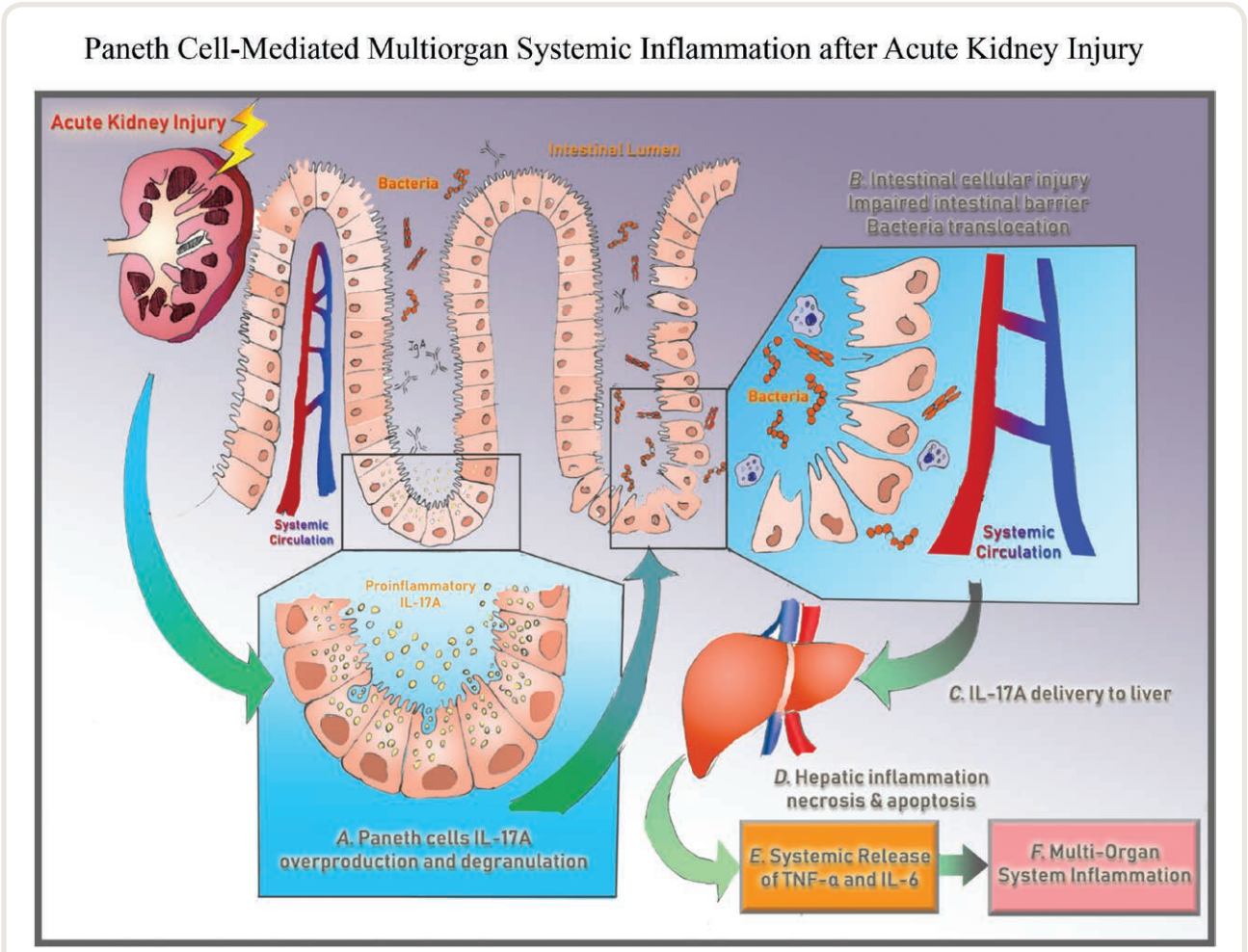

Fig. 3. Paneth cell-mediated multiorgan systemic inflammation after acute kidney injury. Recent experimental studies indicate that acute loss of kidney function (*A*) causes small intestinal Paneth cells in the intestinal crypts to generate and degranulate proinflammatory interleukin (IL)-17A into the intestinal lumen, (*B*) which directly causes intestinal cellular injury and intestinal barrier breakdown. This allows for bacterial translocation and (*C*) portal delivery of IL-17A–containing macrophages, which causes (*D*) hepatic injury and (*E*) hepatic release of IL-6 and tumor necrosis factor (TNF)-α into the circulation, (*F*) leading to further hepatic and systemic inflammation. These studies highlight that acute kidney injury is not merely a bystander but can initiate a downward spiral triggering multiorgan failure and death.[46]

populations.[30,31,40] Furthermore, independent risk factors for perioperative acute kidney injury include advanced age, African American race, preexisting hypertension, active congestive heart failure, chronic kidney disease, pulmonary disease, insulin-dependent diabetes mellitus, peripheral vascular disease, presence of ascites, and high body mass index.[25,29,30,55–62] For example, acute kidney injury prevalence among bariatric surgery cases is around 6 to 8%.[60–62] In addition to being a general risk factor, a high body mass index may increase the risk of perioperative acute kidney injury. It is hypothesized that an increase in oxidative stress, proinflammatory cytokines, and endothelial dysfunction associated with obesity could influence whether a patient develops acute kidney injury.[29,59–62] Conflicting data exist regarding the influence of sex on acute kidney injury occurrence. Within cardiac surgery literature, the evidence is inconclusive with conflicting results that female sex may pose an increased perioperative risk for developing acute kidney injury.[55] However, among general surgery patients, the American College of Surgeons–National Surgical Quality Improvement Program (ACS-NSQIP) 2005 to 2006 national data collection showed that male sex, rather than female, doubles the acute kidney injury threat after general surgery.[58] From a clinical perspective, many of these factors are not modifiable. Identifying these patient-associated comorbidities may help with individual preoperative risk stratification and prevention. Such clinical risk factors may include male sex, particularly in general surgery patients, obesity, advanced age, African American race, preexisting hypertension, active congestive heart failure,

chronic kidney disease, pulmonary disease, insulin-dependent diabetes mellitus, and peripheral vascular disease.

Surgery-associated Risk Factors for Perioperative Acute Kidney Injury

Acute kidney injury is a dangerous complication in both cardiac and noncardiac surgeries and independently associated with emergency surgery.[58] One third of acute kidney injury cases that occurred among patients who are critically ill have a previous history of major surgery.[63]

Acute Kidney Injury in Cardiac and Vascular Surgery

In vascular and cardiac surgeries, acute kidney injury is a well established obstacle. Within these surgical settings, acute kidney injury is correlated with prolonged aortic cross-clamp and ischemia time, the creation of micro- and macroemboli, low cardiac output state, prolonged hypotension, and the use of vasopressors and inotropes. In addition to low mean arterial pressure during cardiopulmonary bypass (CPB), there are reports of contact-activated systemic inflammation, triggered by blood flow across the artificial surface of the bypass circuit. These damaging elements of CPB compromise renal blood flow and lead to renin–angiotensin–aldosterone system activation, decline of renal perfusion pressure, and worsening renal insult.[64] Furthermore, the components of CPB (pump, oxygenator, suction, filters) impose mechanical damage to the circulating erythrocytes, leading to intraoperative hemolysis and release of free hemoglobin. Free hemoglobin can cause direct injury to the renal epithelium *via* generation of free-radical species and obstructive cast formation.[65] Strategies to minimize renal injury with CPB have been explored and include a goal-directed oxygen delivery threshold for adjusting arterial pump flow according to the hematocrit value and when necessary by blood transfusion when thresholds cannot be maintained with increased pump flow.[66] Similar to a goal-directed oxygen delivery strategy, maintenance of a mixed venous oxygen saturation target above 75% during CPB is hypothesized to optimize system perfusion and may be linked with a lower risk of postoperative acute kidney injury.[67] Further investigations are still needed to understand the optimal strategies necessary to reduce acute kidney injury risk during CPB among high-risk cases.

With the apparent renal implications of CPB, it may appear intuitive that off-pump coronary artery bypass would exhibit renal sparing effect compared with the traditional on-pump coronary artery bypass graft (CABG) surgery. To date, however, clear consensus has not been reached. The CABG Off or On Pump Revascularization Study (CORONARY) randomized 4,752 patients from 2006 through 2011 at 79 centers in 19 countries to on-pump or off-pump technique. The study found no significant difference in new renal failure requiring dialysis at 30 days, but a substantial decrease in the incidence of acute kidney injury was observed (28.0% *vs.* 32.1%; relative risk, 0.87; 95% CI, 0.80 to 0.96; $P = 0.01$) in the off-pump group.[68] In contrast, the German Off Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) trial randomized 1,593 elderly patients to either on or off technique from 2008 through 2011 and found that off-pump CABG surgery was not correlated with a decreased incidence or reduced severity of acute kidney injury ($P = 0.174$).[69] Current evidence does not demonstrate a consistent reduction in the relative risk of acute kidney injury or dialysis with an off-pump revascularization technique. Given the lack of supporting evidence, off-pump CABG surgery should not routinely be recommended for all CABG patients at risk of perioperative acute kidney injury, especially in light of associated lower off-pump CABG revascularization success rates.[68,70]

Acute Kidney Injury in Noncardiac Surgery

Occurrence of acute kidney injury among noncardiac and nonvascular surgeries has been studied less extensively than during cardiac surgery, probably because of its overall lower incidence. According to the American College of Surgeons–National Surgical Quality Improvement Program national data collection, complications caused by acute kidney injury occur in approximately 1% of general surgery cases, resulting in an eight-fold increase in all-cause 30-day mortality.[58] Within the general surgery category, intraperitoneal surgery is an established risk for developing perioperative acute kidney injury.[58] Procedure-related factors in abdominal surgery include intraoperative blood transfusions, episodes of intraoperative hemodynamic instability, and the use of vasopressors and diuretics.[28,71] Increase in intraabdominal pressure, often caused by an excessive fluid administration or rapid fluid shift, is predictive of postoperative renal impairment.[72,73] The reduction in perfusion pressure is attributed to mechanical compression of renal vasculature, causing a decreasing renal perfusion pressure and inducing renal ischemia.[72,73] Of note, laparoscopic surgery with transient elevations in intraabdominal pressure caused by pneumoperitoneum may result in a clinical decline in urine output, without causing an increase in postoperative acute kidney injury rates.[29,71]

Diagnosis of Perioperative Acute Kidney Injury

Diagnostic Criteria Utilizing Creatinine and Urine Output

Multiple definitions and measurements to diagnose acute kidney injury have been explored and studied over the past 30 years. Measurements of serum creatinine and urine output remain the foundation of acute kidney injury diagnosis because they are both easily measurable and distinct to the kidney. The Risk, Injury, Failure, Loss, End-stage renal disease and Acute Kidney Injury Network criteria were each developed with the goal of creating a standardized definition of acute kidney injury that would also allow early and

accurate diagnosis and treatment.[12,74] In 2012, the Kidney Disease Improving Global Outcomes classification system emerged and remains the primary classification system for acute kidney injury.[14]

Diagnostic Difficulties in the Perioperative Period

Despite the development of a uniform standard to define acute kidney injury, the Kidney Disease Improving Global Outcomes classification system still has recognized limitations, particularly in the perioperative period. Urine output is a sensitive detection tool for identifying acute kidney injury and is appropriately included in all acute kidney injury definitions. However, the perioperative period has shown to be a unique environment with its own diagnostic challenges. Studies have shown that urine output frequently is decreased in the intraoperative and postoperative period because of the release of aldosterone and vasopressin from stress, hypovolemia, or even anesthesia.[75,76] A 2010 study noted that during surgery, only 5 to 15% of a crystalloid volume load is excreted in the urine, as opposed to 40 to 75% in a nonanesthetized patient.[75] This decrease in urine output was unchanged whether the anesthesia was performed using isoflurane or a propofol infusion. Several studies have examined the relationship between fluid administration and intraoperative urine output and its correlation with postoperative acute kidney injury. One such randomized prospective study examined 102 patients undergoing bariatric surgery who received either high- or low-volume amounts of lactated Ringer's solution.[76] The authors failed to find a correlation between low urine output in the intraoperative period and postoperative acute kidney injury.[76] In conclusion, urine output is a less useful criterion for diagnosing perioperative acute kidney injury, necessitating a need for other diagnostic methodologies.

Serum creatinine is also a flawed diagnostic tool and can be an inaccurate marker for glomerular filtration rate. As a primary diagnostic criterion for acute kidney injury, serum creatinine is problematic because of the temporal delay from injury to the necessary diagnostic rise in creatinine. Creatinine will begin to rise after the glomerular filtration rate is decreased by 50%.[77] An initial creatinine rise may occur on postoperative day 1; however, the clear majority of patients fail to meet criteria for acute kidney injury until postoperative day 2. Because of this "creatinine blind window of acute kidney injury," perioperative acute kidney injury is frequently recognized late in the kidney injury process. Serum creatinine can also be altered by a variety of other factors than kidney junction, many of which are common in the perioperative period, including muscle injury, volume overload, nutrition, and steroids.[77] In summary, the clinical practice of predominantly basing the clinical diagnosis of acute kidney injury on measurements of serum creatinine has many limitations, such as a delay in diagnosing early stages of acute kidney injury. Research into the efficacy of novel biologic markers is ongoing to improve the identification and treatment of acute kidney injury.

Novel Acute Kidney Injury Biomarkers

The utility of biomarkers as reliable measurement tools for detecting minor but significant renal injury has been a focus of translational and bench research. As shown in Supplementary Digital Content 2 (http://links.lww.com/ALN/C56), there are numerous ongoing clinical trials to further sharpen our view and clinical approaches for novel acute kidney injury biomarkers (Supplementary Digital Content 2, http://links.lww.com/ALN/C56). A highly precise biomarker would be ideal for renal injury and sensitive from insult to resolution (*e.g.*, accounting for the "creatinine blind" window). Currently, biomarkers showing the most promise all have differing levels of sensitivity and specificity for acute kidney injury, with vastly differing time courses. They are described in more detail below (fig. 4).[78]

The neutrophil gelatinase-associated lipocalin molecule is absent in the urine and plasma of healthy individuals. The molecule was initially discovered in a screening study that was designed to identify genes that are differentially expressed in the early periods after renal ischemia. By clamping the renal artery in mice for 45 min, cDNA microarrays were used to define changes in renal gene expression. The authors identified seven upregulated genes, including neutrophil gelatinase-associated lipocalin, an easily measurable stable polypeptide found in the urine during the kidney injury process.[79,80] However, point-of-care testing is unable to detect the renal isoform of neutrophil gelatinase-associated lipocalin. Initial studies showed promise as a predictive indicator of acute kidney injury within cardiac surgery cases, where urine neutrophil gelatinase-associated lipocalin levels are diagnostic of acute kidney injury at 2 h postcardiac bypass.[78,80] In a pediatric trial, similar findings in CPB patients were observed with neutrophil gelatinase-associated lipocalin levels elevated in acute kidney injury patients within 2 h, compared with 1 to 3 days for diagnostic creatinine levels.[81] Criticism of these early neutrophil gelatinase-associated lipocalin trials was the homogenous study population and comorbidity exclusion criteria.[81–83] Subsequent studies with heterogeneous surgical populations found no association between neutrophil gelatinase-associated lipocalin and acute kidney injury.[84,85] An examination of noncardiac surgery cases, showed higher levels of urine and serum neutrophil gelatinase-associated lipocalin among those who have diabetes mellitus, an infection, and chronic kidney disease but failed to correlate an association between neutrophil gelatinase-associated lipocalin levels and acute kidney injury.[84] Specificity of neutrophil gelatinase-associated lipocalin has been estimated to range between 70 to 80%; however, sensitivity is unpredictable, varying from 40 to 90%.[78] The reason for such discrepancy is uncertain. However, neutrophil gelatinase-associated

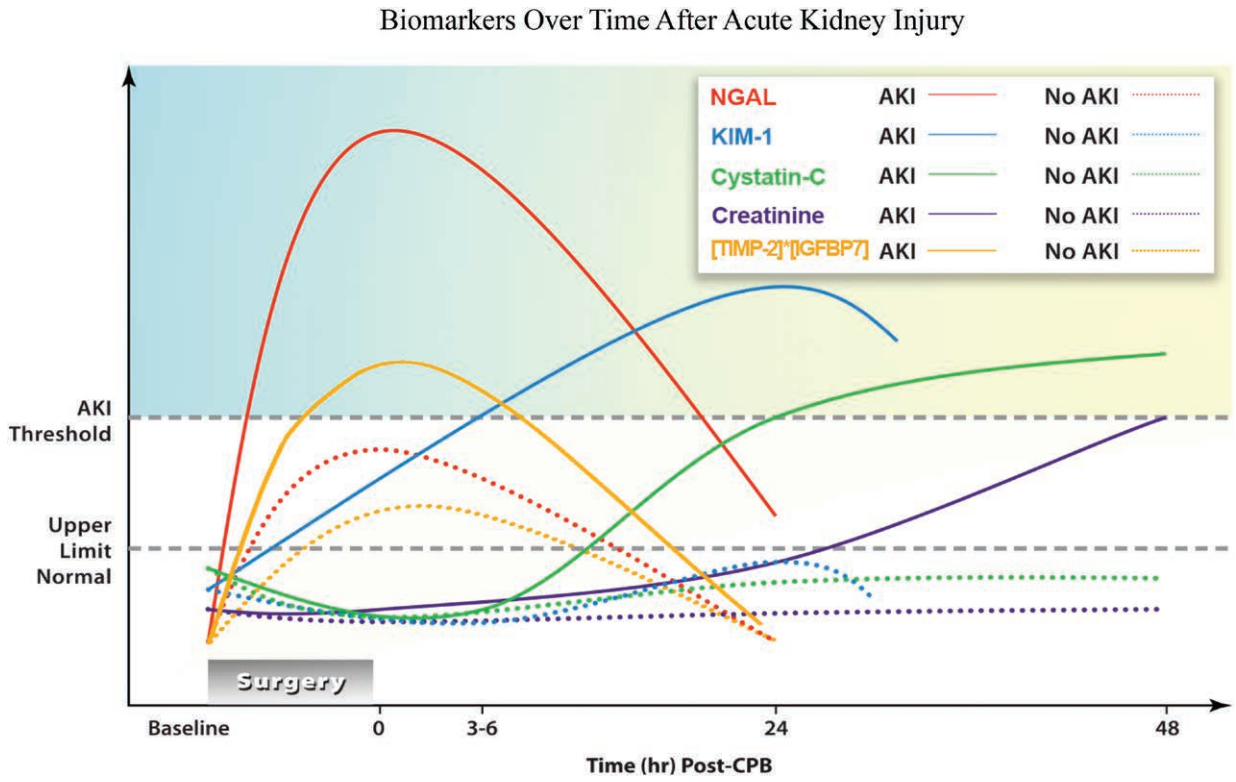

Fig. 4. Biomarkers over time after acute kidney injury (AKI). Schematic representation of the levels of several biomarkers over time. The baseline (time 0) is immediately after cardiac bypass (CBP). The *lines* are a schematic of the predicted rise and fall of the biomarkers after CBP as a function of time and when levels become significant enough to cross the threshold for diagnosing AKI. These patterns and specifically the timeline for diagnosing AKI represent ideal circumstances (the shortest possible time interval shown in a clinical study) and not necessarily what will prove to be clinically verifiable. Cystatin-C, serum cystatin C; IGFBP7, insulin-like growth factor binding protein 7; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinase 2. Reprinted with permission.[78]

lipocalin levels may be affected by a wide range of factors, such as infections, certain tumors, cardiovascular disease, preexisting renal disease, age, and diabetes mellitus. The influence of confounding variables has raised concerns regarding its diagnostic performance.[86,87] Research is still ongoing for neutrophil gelatinase-associated lipocalin with several studies evaluating opportunities in contrast-induced nephropathy and utilizing neutrophil gelatinase-associated lipocalin to project whether there will be a need for renal replacement therapy.[88,89] Better defining which patient populations will benefit from neutrophil gelatinase-associated lipocalin as a diagnostic tool and its role in combination with other biomarkers is the next step in the research of this important protein.

Another promising biomarker is kidney injury molecule-1. Kidney injury molecule-1 is a type-1 membrane glycoprotein that is upregulated after an ischemic or nephrotoxic injury to the proximal tubule epithelial cells.[90] Studies show that kidney injury molecule-1 functions as a cell adhesion molecule in the reconstruction of injured proximal tubules.[78] A trial examining the occurrence of acute kidney injury during cardiac surgery in pediatric cases found kidney injury molecule-1 to be an excellent diagnostic molecule with elevated urine levels within 6 h after cardiac bypass.[91] However, another study in adult cardiac surgery patients showed good specificity but a sensitivity of only 50% when using urinary kidney injury molecule-1 to diagnose acute kidney injury.[92] This study, along with others, showed that kidney injury molecule-1 is potentially more useful when used as part of a panel combining several biomarkers.[91,92] However, there is currently no point-of-care device in the marketplace for immediate assessment of kidney injury molecule-1.

Cystatin C is unique in that it is a very small, charged molecule completely filtered at the glomerulus where it undergoes catabolism by proximal tubule cells. Because of this, there is virtually no measurable cystatin C found in the urine of healthy kidneys.[78] The above characteristics and a short half-life in the serum (2 h) have made several investigators propose that serum cystatin C is an ideal surrogate

for glomerular filtration rate and tubular cell integrity.[78,93–95] Two studies examining the use of serum cystatin C have had mixed results, with one showing its ability to diagnose acute kidney injury occurring within 6 h after surgery, whereas the other found it to be no better than creatinine.[92,93] However, this study did show that urine cystatin C levels rose within 6 h after bypass in those with acute kidney injury, necessitating further study to clarify its role.[96] Currently, the number of patients studied utilizing cystatin C is small, making the results and future of this molecule as a novel acute kidney injury biomarker still to be seen.

Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 get released during cell cycle arrest and could potentially present sensitive and precise biomarker molecules for diagnosing acute kidney injury.[97] During normal cell proliferation, a cell must go through each stage of the cell cycle (G_1–M).[98] However, when cells are damaged, they utilize cell cycle arrest as a protective mechanism to circumvent replication of damaged DNA.[98] When renal cells enter cell cycle arrest, this adaptive response is mediated by surrounding cells through the release of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7.[98] Their presence in the urine is hypothesized to be one of the earliest signs of cellular kidney damage.[97,98] Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 biomarkers were identified and consequently confirmed in the second phase of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, which examined samples from over 700 patients across 35 centers.[97,98] Univariate analysis showed that tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 levels of more than 2.0 ([ng/ml] 2/1000) correlated to an elevated risk of all-cause mortality or renal replacement therapy (hazard ratio, 2.11; 95% CI, 1.37 to 3.23; $P < 0.001$). In a multivariate analysis adjusted for the clinical model, tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 levels of more than 0.3 ([ng/ml] 2/1000) were associated with death or renal replacement therapy among subjects who developed acute kidney injury.[97] The SAPPHIRE trial also determined that the combination of the two biomarkers proved to be of greater prognostic value for acute kidney injury than either in isolation. Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 was appreciably more predictive to previously described markers of acute kidney injury ($P < 0.002$), such as neutrophil gelatinase-associated lipocalin and kidney injury molecule-1, in a heterogeneous population.[98] A recent meta-analysis found they accurately predicted the probability to develop acute kidney injury and subsequent necessity for renal replacement therapy with a sensitivity and specificity of 0.69 and 0.81, respectively.[99] These numbers are promising and will be the focus of several upcoming translational studies to determine its clinical application.

Although several studies were able to demonstrate a statistical association between biomarker level and acute kidney injury, it has been more difficult to prove that biomarker measurements alter clinical outcomes. A recent study comparing the use of a furosemide stress test (which involves giving an IV dose of furosemide followed by 2 h of close urine output monitoring) was equally or more effective at predicting acute kidney injury and necessity of renal replacement therapy than several biomarkers, including neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7.[100] This shows that we should not necessarily forget about previously used methods of acute kidney injury diagnosis, such as urine output and creatinine, but can potentially find other modalities to complement and enhance their diagnostic capability. This is especially true in the perioperative period, during which urine output cannot be relied on as an accurate indicator of acute kidney injury.

The future of biomarkers remains an active and dynamic area of intense research, with translational studies merging biomarker "panels" with existing diagnostic criteria to improve detection and intervention. A promising recent study examined several renal biomarkers, including kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, and cystatin C, and failed to show that any of them alone were better at predicting the necessity of renal replacement therapy or hospital mortality than changes in creatinine.[101] However, when the biomarkers were combined, along with a measure of change in creatinine, they could predict adverse events with excellent sensitivity and specificity. NephroCheck (Astute Medical, USA) was authorized by the U.S. Food and Drug Administration in 2014 as a point-of-care urinary biomarker assay to evaluate acute kidney injury development.[102] This *in vitro* urine assessment quantitatively measures tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 with reference intervals established in healthy adults and stable chronic morbid conditions without preexisting acute kidney injury.[102,103] Daubin *et al.*[104] evaluated the NephroCheck in critically ill patients and determined acute kidney injury patients have a significantly higher score than patients without acute kidney injury (0.43 [0.07 to 2.06] *vs.* 0.15 [0.07 to 0.35]; $P = 0.027$). However, the authors noted that NephroCheck was unable to distinguish between temporary and persistent acute kidney injury.[104]

The future of point-of-care testing is bright, but significant confounding hurdles must be accounted for to validate the integration of point-of-care testing with biomarker panels. As more biomarkers become commercially available, translational research is necessary to evaluate the efficacy of biomarker panels and point-of-care testing to allow for early intervention, risk assessment, and diagnosis of acute kidney injury.

Therapeutic Approaches for Perioperative Acute Kidney Injury

Developing successful therapies to treat acute kidney injury has been an elusive endeavor. Despite significant

advancements in diagnosis, surgical techniques, anesthetic methods, and critical care management, the frequency of perioperative acute kidney injury has remained essentially unchanged.[105] Although numerous agents have shown promise, a single strategy toward improving treatment options for acute kidney injury has failed to demonstrate utility in clinical care.[106–109] This continues to be an area of intense research with numerous ongoing translational and clinical trials (Supplementary Digital Content 3, http://links.lww.com/ALN/C57). Moreover, many exciting recent studies have found important concepts that are critical for patient management in acute kidney injury prevention.

Pharmacologic Interventions

Pharmacologic interventions to effectively treat and prevent acute kidney injury have been evaluated extensively across perioperative environments including major nonvascular, cardiovascular, contrast-induced acute kidney injury, and intensive care units. In addition, there is a substantial number of ongoing clinical trials to define and evaluate pharmacologic interventions in the perioperative setting (Supplementary Digital Content 4, http://links.lww.com/ALN/C58). Historically, evidence for pharmacological intervention decreasing rates of acute kidney injury has largely been unsupported by quality data. More recent pharmacologic research has investigated the potential benefit of antiinflammatory, antiapoptotic, and antioxidative interventions to prevent and treat acute kidney injury.

N-Acetylcysteine is a precursor of intracellular glutathione that reduces the oxidative burst response of neutrophils by improving oxygen free radical scavenging.[110] In prospective randomized controlled trials, intravenous *N*-acetylcysteine failed to prevent postoperative renal dysfunction or reduce mortality rates in high-risk CPB surgery patients.[111] Similarly, a double-blinded randomized controlled trial by Song *et al.*[112] failed to establish a protective benefit of *N*-acetylcysteine in off-pump CPB surgery, with similar rates of acute kidney injury observed between treatment and control groups (35% *N*-acetylcysteine *vs.* 32% control; $P = 0.695$). The antioxidative benefit of allopurinol and supplements such as selenium, zinc, and vitamins C, E, and B1 have also failed to show benefit in clinical trials.[113,114] Current evidence does not support the role of *N*-acetylcysteine or supplements such as selenium, zinc, and vitamins C, E, and B1 to prevent acute kidney injury.[111,113–115]

The lipid-lowering 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins are a drug class with increasing research interest because of their potential anti-inflammatory, antioxidative, and endothelial protective properties.[29,116,117] A 2018 study involving eight randomized controlled trials investigated the effect of cardiac surgery-associated acute kidney injury and perioperative statin therapy but did not find a correlation between statin administration and acute kidney injury reduction (relative risk 1.17; 95% CI, 0.98 to 1.39; $P = 0.076$). Statin administration both pre- and postsurgery actually increased acute kidney injury risk when compared with preoperative statin therapy alone ($P = 0.040$).[118] A meta-analysis by Zhao *et al.*[117] suggests that sufficient evidence has accrued to reject the hypothesis that perioperative statin therapy decreases the prevalence of acute kidney injury and secondary postoperative consequences such as renal replacement therapy, mechanical ventilation, length of stay in the intensive care unit (ICU) or hospital, and in-hospital death. In summary, the present evidence does not substantiate using statin therapy in the treatment or prevention of acute kidney injury.

Dexmedetomidine, a selective α2-adrenergic receptor agonist, was another candidate agent for perioperative kidney protection through increasing renal blood flow and also decreasing oxidative insult to the kidney. In animal models, dexmedetomidine has demonstrated antiinflammatory, antiapoptotic, and antioxidative properties across organ systems.[119–122] Several studies have also demonstrated inhibition of inflammatory mediators including interleukin-1, interleukin-6, and TNF-α.[123,124] The clinical application of dexmedetomidine's renoprotective properties has successfully reduced the incidence of cardiac surgery-associated acute kidney injury in valvular heart surgery populations.[125–128] The presumed beneficial effect includes a reduction in norepinephrine release, enhanced hemodynamic stability, and myocardial oxygen supply/demand balance.[29] In a recent meta-analysis involving 19,266 patients, dexmedetomidine was found to lower rates of cardiac surgery-associated acute kidney injury in both randomized controlled trials (relative risk, 0.44; 95% CI, 0.26 to 0.76; $P = 0.003$) and cohort studies (relative risk, 0.74; 95% CI, 0.63 to 0.86; $P = 0.0001$).[129] However, dexmedetomidine failed to decrease postoperative mortality, duration of mechanical ventilator, and length of stay in the ICU or hospital.[129] Based on these studies, dexmedetomidine may have the capacity to attenuate acute kidney injury in surgical patients. However, additional high-quality, multicenter trials will have to confirm these findings to establish the basis for its routine clinical use to prevent perioperative acute kidney injury.[29] Beyond pharmacologic intervention, opportunities for nonpharmacologic therapy such as remote ischemic preconditioning and renal replacement therapy have been researched extensively to treat and prevent acute kidney injury.

Remote Ischemic Preconditioning

Ischemic preconditioning is an experimental strategy in which short, nonlethal episodes of ischemia are applied to provide protection from a subsequent, more lethal ischemic insult.[42,130,131] As a more recently discovered form of ischemic preconditioning, remote ischemic preconditioning is achieved through application of brief periods of ischemia and reperfusion of remote tissues or organs, resulting in the protective adaptive response of distant organ systems. Usually, a blood pressure cuff is placed around the upper arm is inflated to 200 to 300 mm Hg pressure for a 5-min

duration, and then the pressure is released, followed by several repeat cycles. Remote ischemic preconditioning is thought to activate several pathways including systemic antiinflammatory, neuronal, and humoral signaling pathways.[132] In this regard, remote ischemic preconditioning offers a novel, noninvasive, and inexpensive strategy to decrease the occurrence of acute kidney injury.[132–134]

Clinically, some controversy exists regarding the effectiveness of remote ischemic preconditioning on acute kidney injury. The outcomes of remote ischemic preconditioning on the kidney has been investigated extensively within the framework of adult vascular and cardiac surgery. In a large multicenter, randomized double-blind clinical trial, Zarbock *et al.*[134] recently found that remote ischemic preconditioning before cardiac surgery in high-risk patients was effective for decreasing the rate of acute kidney injury (37.5% *vs.* 52.5%) compared to sham (absolute risk reduction, 15%; 95% CI, 2.56 to 27.44; $P = 0.02$). In addition, a subsequent long-term follow up by the same authors revealed remote ischemic preconditioning lowered the 3-month prevalence of a composite endpoint of major adverse kidney events consisting of death, necessity of renal replacement therapy, and chronic renal dysfunction.[135] These findings are supported by similar randomized controlled trials in the cardiac and vascular literature conducted by Ali *et al.*[136] and Thielmann *et al.*[137] Despite these exciting findings, the discussion of remote ischemic preconditioning and kidney protection remains inconclusive with other postcardiac surgery outcomes trials unable to establish a protective effect.[138–140] The differences in these outcomes could be related to study design (*e.g.*, the selection of primary endpoints), different patient populations (high risk *vs.* lower risk of acute kidney injury), or the specific protocol used for remote ischemic preconditioning. Additionally, anesthetic type may alter the effect of remote ischemic preconditioning, with reports of propofol blunting the observed beneficial effects relative to volatile anesthetics.[141,142] Because of the very noninvasive nature, unknown side effects, and promising initial findings, the threshold to introduce remote ischemic preconditioning into routine clinical practice is relatively low. Nevertheless, further multicenter trials are needed to fully establish the clinical benefits, dose, and ideal patient population for remote ischemic preconditioning therapy to prevent acute kidney injury in surgical patients.

Renal Replacement Therapy

Renal replacement therapy is the only therapy for acute kidney injury to date. The Kidney Disease Improving Global Outcomes criteria advocate initiating renal replacement therapy when fluid accumulation becomes life-threatening or major imbalances (*e.g.*, acidosis, electrolyte abnormalities, and uremia) occur.[29,143] The ideal mode of renal replacement therapy, the correct timing of when to begin therapy, and the duration are still under debate.[29] A recent meta-analysis evaluating renal replacement therapy modalities on clinical outcomes failed to find statistical differences for the pooled mortality results (ICU, in-hospital, or 30-day) and dialysis dependence between continuous renal replacement therapy and sustained low efficiency dialysis.[144] Clinical studies to address the exact timing of when to initiate renal replacement therapy show conflicting data as well. Two large prospective randomized controlled trials, the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial and the Early *versus* Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury (ELAIN) trial, evaluated the influence of renal replacement therapy timing in ICU patients with acute kidney injury.[145–147] The Early *versus* Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury trial reported that early initiation of renal replacement therapy in patients suffering from acute kidney injury resulted in a significant reduction in 90-day mortality. This is in contrast to the Artificial Kidney Initiation in Kidney Injury trial, which failed to show a reduction in mortality as a function of renal replacement therapy timing.[145–147] Most recently, the Initiation of Dialysis Early *versus* Delayed in the Intensive Care Unit (IDEAL-ICU) trial examined a relatively homogenous population of patients with early-stage septic shock who had severe acute kidney injury.[148] In this multicenter randomized trial, patients with early sepsis were randomized to early (within 12 h) or delayed initiation (delay of 48 h) of renal replacement therapy. The trial was stopped early after an interim analysis. In this group of patients, early initiation of renal replacement therapy failed to demonstrate a lowering of mortality at 90 days, compared with the delayed initiation of renal replacement. Importantly, there was overall less use of renal replacement therapy in the delayed-strategy group, because 75% of patients in the delayed group recovered their kidney function spontaneously. However, it is important to keep in mind that starting treatments late in the chain of acute kidney injury (*e.g.*, at the stage of severe acute kidney injury) does not improve patient outcomes. Therefore, it is important that we detect patients who suffer from a progressive form of acute kidney injury early. In addition, the Acute Disease Quality Initiative (ADQI) workgroup suggested a more personalized approach should be considered for initiation of renal replacement therapy, based on the dynamic assessment of different clinical parameters that reflect the mismatch of demand and capacity.[149] Based on the conflicting results from these trials, there continues to be a need for additional research to reduce the variability of timing in the initiation of renal replacement therapy.[149]

Fluid Replacement Approaches

The administration of fluids is a mainstay of therapy to prevent hypovolemia and improve renal perfusion. However, the debate of restrictive *versus* liberal fluid therapy has been an ongoing argument among perioperative physicians for many decades. Historically, conventional regimens were characterized by the liberal administration of large intravenous fluid volumes (*e.g.*, more than 7 l for open abdominal surgery)

to account for fluid deficits, vasodilation, hemorrhage, and fluid accumulation in extravascular spaces.[150,151] However, with the introduction of Enhanced Recovery After Surgery (ERAS) protocols, a more restrictive pattern of fluid administration has been proposed with the benefit of fewer complications (*i.e.*, pulmonary, acute kidney injury, sepsis, and wound healing), shorter time to recovery, and shorter length of hospital stay.[152–156] To investigate the outcome of liberal *versus* restrictive fluid administration in the perioperative patient, the Restrictive *versus* Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial was conducted in 2018.

The Restrictive *versus* Liberal Fluid Therapy in Major Abdominal Surgery trial was an international, randomized, assessor-blinded trial that compared a restrictive intravenous fluid regimen to a liberal regimen in 3,000 patients undergoing major abdominal surgery.[151] The median intravenous fluid intake for the group with restricted fluid was 3.7 l *versus* 6.1 l in the liberal fluid group.[151] They found that a regimen consisting of restricted fluid intake had no correlation with higher rates of disability-free survival than a regimen of liberal fluid intake. However, the study did find that a restricted fluid regimen was correlated to higher rates of acute kidney injury (8.6% restrictive *vs.* 5.0% liberal fluid group [$P < 0.001$]).[151] Brandstrup,[157] in the editorial response to the Myles *et al.*[151] Restrictive *versus* Liberal Fluid Therapy in Major Abdominal Surgery trial, eloquently surmised that "a modestly liberal administration of balanced salt solutions does not create substantial fluid retention, and it appears to be safe to administer a fluid volume that slightly exceeds zero fluid balance, although patients for whom an ERAS protocol is used might not need it. In addition, we learn that physiologic principles remain valid: both hypovolemia and oliguria must be recognized and treated with fluid."[157] Based on these findings, a reasonably liberal fluid intake regimen is potentially safer than a highly restricted fluid intake regimen for fluid resuscitation of the perioperative patient.[157]

Goal-directed Hemodynamic Therapy

Maintaining volume status and perfusion pressure are central tenants of the Kidney Disease Improving Global Outcomes recommendations. Early goal-directed hemodynamic therapy was proposed to optimize fluid resuscitation and cardiac output to improve microvascular perfusion pressure and cellular oxygenation while minimizing the harmful effects of fluid overload.[107,158–161] Goal-directed hemodynamic therapy, predefined algorithms of fluid loading, and inotropic support are utilized to account for variables such as myocardial performance,[162,163] vascular tone, regional blood flow distribution,[164] venous reservoir capacity, and capillary permeability.[165] A recent randomized controlled trial, the Optimization of Cardiovascular Management to Improve Surgical Outcome trial (OPTIMISE), was conducted to analyze the virtues of using goal-directed therapy to prevent acute kidney injury in noncardiac surgical populations.

The Optimization of Cardiovascular Management to Improve Surgical Outcome trial was a pragmatic, multicenter, randomized, observer-blinded trial of 734 high-risk patients. Patients were over the age of 65 undergoing major gastrointestinal surgery with the presence of cardiac or respiratory disease, renal impairment (serum creatinine levels of at least 1.5 mg dl^{-1}), or diabetes mellitus or undergoing emergency surgery.[166] Patients were randomized to standard of care or a cardiac output–guided hemodynamic therapy algorithm for intravenous fluid and inotrope support during and after surgery.[166] Patients receiving intervention had a relative risk of 0.84 (95% CI, 0.71 to 1.0) and an absolute risk reduction of 6.8% (95% CI, −0.3% to 13.9%; $P = 0.07$).[166] There was no difference in the secondary outcomes of 7-day morbidity, critical care days, all-cause mortality at 30 and 180 days, or acute hospital length of stay.[166] The question of whether goal-directed therapy improves postoperative outcome is still under debate. Gelman and Bigatello[167] attribute the inconsistent benefits to an infused fluid volume that serves only to increase the unstressed capacity, whereas the stressed volume and hemodynamics remain largely unchanged. Further, variability is influenced by type of hemodynamic monitor, fluid administered algorithms, as well as the type and duration of hemodynamic intervention. Multicenter randomized controlled trials are needed to understand the role of goal-directed therapy in acute kidney injury outcomes. Based on these studies, the value of using goal-directed hemodynamic monitoring approaches to guide specific algorithms for fluid replacement remains questionable. Even in today's world, perioperative physicians may still be faced with the challenge of utilizing best clinical judgment in a complex clinical environment to make decisions about hemodynamic optimization of surgical patients.

Impact of Intravenous Fluid Composition

In line with the previous discussion of hemodynamic optimization, an ongoing argument in the field focuses on the type of fluid used in resuscitation. Isotonic crystalloid remains the standard for first-line resuscitation fluid therapy in the perioperative and ICU environments. Globally, the most frequently employed isotonic crystalloid is 0.9% sodium chloride. However, accumulating evidence suggests patients are at risk of adverse effects to acid–base homeostasis, renal vasoconstriction, reduced glomerular filtration rate, increased risk of acute kidney injury, and death.[168–173] Based on this research, a supraphysiologic chloride concentration of saline could be a potential contributor to kidney injury.[174] Two large-scale studies investigated the effect of balanced crystalloids and saline in critical and noncritical populations: the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), examined using balanced crystalloids *versus* saline in patients in medical (SMART–MED) and nonmedical (SMART–SURG) ICUs; and the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT–ED) trial.[174,175]

The SALT-ED trial was a single-center, pragmatic, multiple-crossover study comparing balanced crystalloids with saline in 13,347 adults treated with intravenous crystalloids during hospitalization outside of the ICU environment.[174] There was not a significant difference between the two groups in the number of hospital-free days. However, there was a lower prevalence of major adverse kidney events in the balanced crystalloids group (4.7% *vs.* 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; $P = 0.01$).[174] In this trial of noncritically ill adult patients, balanced crystalloid treatment did not result in reduced time to hospital discharge, but it did find there was a lower prevalence of composite death, new renal replacement therapy, and chronic renal dysfunction.[174]

The SMART trial was a pragmatic, cluster-randomized, multiple-crossover design study of 15,802 ICU adult patients who received either 0.9% sodium chloride or balanced crystalloid solutions.[175] Similar to the SALT-ED trial, the main outcomes were major adverse kidney events within 30 days, new renal replacement therapy, or chronic renal dysfunction.[175] A major adverse kidney event occurred in 14.3% of the study population who received balanced-crystalloid solutions, and in the cohort who received 0.9% sodium chloride solution, 15.4% suffered from a major adverse kidney event (marginal odds ratio 0.91; 95% CI, 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; $P = 0.04$).[175] Among critically ill adults, using balanced crystalloids lowered death rates from any cause, new renal replacement therapy, or chronic renal dysfunction.[175] Based on these recent, high-quality clinical trials, a balanced crystalloid solution with electrolyte compositions comparable with plasma is preferred for volume resuscitation to minimize adverse kidney events and death.[29]

In a classical view of microvascular fluid dynamics, colloids were hypothesized to be more effective than crystalloids in reestablishing circulating plasma volume, because their volume of distribution was thought to be comparatively maximized within the intravascular compartment, reducing time to hemodynamic stability with a comparatively smaller volume, with an effective longer duration. Through the investigation of crystalloid resuscitation alternatives, various controlled studies have scrutinized the efficacy of albumin, hydroxyethyl starch, and gelatin-based colloids.

The Crystalloid *Versus* Hydroxyethyl Starch Trial (CHEST) and Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial were landmark trials that compared the effects of resuscitation with hydroxyethyl starch and crystalloid solutions.[176,177] Findings from these trials demonstrate an association of acute kidney injury risk, increased rate of renal replacement therapy, and death with hydroxyethyl starch among ICU and septic patient populations.[176,177] These findings led drug regulators in Europe and the United States to issue black box safety warnings in 2013 against the use of hydroxyethyl starch. However, the use of hydroxyethyl starch-containing solutions remains controversial. As Weiss *et al.*[178] recently highlighted, "every drug can be used safely and effectively when it is used appropriately, according to its indication and in the right patient population." Currently, two prospective, randomized, controlled, double-blind trials are underway, the Safety and Efficacy of 6% Hydroxyethyl Starch (HES) Solution *versus* an Electrolyte Solution in Patients Undergoing Elective Abdominal Surgery (PHOENICS) trial (NCT03278548) and the Safety and Efficacy of a 6% Hydroxyethyl Starch (HES) Solution *versus* an Electrolyte Solution in Trauma Patients (TETHYS) trial (NCT03338218). Hydroxyethyl starch should be administered with caution in critically ill patients until new evidence from these ongoing trials is made available.

After concerns were raised about the safety profile of hydroxyethyl starch, a renewed interest in the safety and efficacy of gelatin and albumin colloid alternatives occurred in the marketplace. The use of albumin, a natural colloid, is an effective plasma volume expander and has been shown to improve microcirculation.[179,180] In the Saline *versus* Albumin Fluid Evaluation (SAFE) trial, a double-blinded randomized controlled trial, there was no observed difference in urine output, organ failure, and duration of renal replacement therapy between saline and 4% albumin solutions. Although albumin appears safe, it is two to five times more expensive than crystalloid and offers no significant difference in patient outcomes.[181] Another colloid alternative to crystalloid extensively utilized worldwide is gelatin, a degradation product of collagen. Gelatin-based solutions are similarly costly (more than 10 times more costly than crystalloid) with evidence of safety and efficacy from large prospective randomized controlled trials surprisingly limited.[182] Moeller *et al.*[183] found risk ratios after gelatin administration were 1.15 (95% CI, 0.96 to 1.38) for mortality, 1.10 (0.86 to 1.41) for requiring allogeneic blood transfusion, 1.35 (0.58 to 3.14) for acute kidney injury, and 3.01 (1.27 to 7.14) for anaphylaxis. Like hydroxyethyl starch, the authors concluded an increased risk of mortality, renal failure, anaphylaxis, and coagulation impairment with gelatin administration.[183] A novel prospective, double-blind randomized controlled trial (NCT02715466) is investigating the therapeutic value and safety of gelatin in patients with early severe sepsis or septic shock. Considering cheaper and safer crystalloid alternatives, the administration of gelatins should be undertaken with caution until further evidence from a well designed trial supporting its use is made available.

Impact of Anemia and Transfusion on Perioperative Acute Kidney Injury

Preoperative anemia, defined by the World Health Organization as less than 12 g/dl for female patients and less than 13 g/dl for male patients, is linked with perioperative acute kidney injury in both cardiac and noncardiac surgery patients.[184–186] Early postoperative decrements in hemoglobin level have also been linked with acute kidney injury.[184] Anemia leads to a state of decreased oxygen-carrying capacity, putting the vulnerable renal medulla at an increased risk of

hypoxic injury. An anemic state also imposes greater oxidative stress on the renal tubules, in part because of the inherent protective function of red blood cells.[186] In addition to preoperative anemic state, perioperative blood transfusion has also been recognized as an independent risk factor for perioperative acute kidney injury. The deleterious effect of allogeneic transfusion has been attributed to the preservation and storage effect of red blood cells, promoting oxidative stress and a proinflammatory state.[186] It is important to note that both anemia and transfusion are associated with acute kidney injury. Measures to optimize a patient's overall preoperative status while minimizing surgical bleeding should be employed to reduce hematologic related acute kidney injury risk.

Avoidance of Nephrotoxic Drugs

Nephrotoxin-induced acute kidney injury is a considerable risk to patients in the perioperative period. Avoidance and minimizing the duration of exposure of these agents reduces the risk of acute kidney injury development.[29] Goldstein *et al.*[187] performed a prospective analysis of implementing an electronic health record screening and decision matrix at Cincinnati Children's Hospital, Cincinnati, Ohio. In 1,749 patients, implementation of a surveillance system reduced the exposure rate and acute kidney injury rate by 38% and 64%, respectively.[187] As highlighted in these studies, scrutinizing for nephrotoxic exposure has the potential to reduce avoidable harm and can help to prevent perioperative acute kidney injury.

Glycemic Control and Nutritional Support

Like nephrotoxic exposure, glycemic control and nutritional support are modifiable, independent predictors of outcome that should be optimized in the perioperative patient. In epidemiological studies, protein-calorie malnutrition is a significant risk factor for in-hospital death among patients suffering from acute kidney injury.[188] Such patients frequently have accelerated protein breakdown and increased caloric needs, especially if they are critically ill or undergoing renal replacement therapy.[26] Piggot *et al.*[189] retrospectively reviewed records of neonates who underwent congenital heart surgery at Arnold Palmer Hospital for Children in Orlando, Florida. In a multivariable analysis, an inability to reach caloric goal preoperatively was independently associated with stage 2 or 3 acute kidney injury ($P = 0.04$; odds ratio, 4.48; 95% CI, 1.02 to 19.63).[189] Further, a difference in peak lactate ($P = 0.002$), inotropic score ($P = 0.02$), and duration of mechanical ventilation ($P = 0.013$) was also observed.[189] Nutrition is fundamental for cellular and organ function, with malnutrition potentially worsening the severity of illness and contributory to acute kidney injury. Similarly, hyperglycemia is considered one of the best independent predictors of mortality and worse outcomes.[190] The Kidney Disease Improving Global Outcomes criteria recommend maintaining blood glucose concentrations between 110 and 149 mg/dl in critically ill patients to minimize perioperative hyperglycemia associated with increased mortality, surgical complications, and acute kidney injury risk.[188] The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE–SUGAR) trial investigated restrictive blood glucose targets.[191] This parallel-group randomized controlled trial demonstrated a higher mortality in ICU patients with restrictive targets (odds ratio, 1.14; 95% CI, 1.02 to 1.28; $P = 0.02$) without reducing the prevalence of acute kidney injury. Based on the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation trial and subsequent meta-analysis, it seems practical to adopt higher glycemic values, avoiding the inherent risks of hypoglycemia associated with tight glycemic benchmarks. Practical targets should be in accordance with the 2012 guidelines set forth by the Kidney Disease Improving Global Outcomes (110 to 149 mg/dl) or the statement from the European Renal Best Practice based on guidelines from the Kidney Disease Improving Global Outcomes (140 to 180 mg/dl).[143,188]

Preventative Acute Kidney Injury Bundle Protocols

The effectiveness of implementing preventative measures such as nutritional support and glycemic control, minimizing nephrotoxic medication exposure, and hemodynamic optimization have largely been studied independently. In 2017, a randomized controlled trial was conducted to analyze the value of implementing a "Kidney Disease Improving Global Outcomes bundle" in cardiac-associated acute kidney injury. In the trial, Meersch *et al.*[192] implemented a Kidney Disease Improving Global Outcomes protocol to optimize intravascular volume and hemodynamics, minimize nephrotoxic exposure, and prevent hyperglycemia in 882 high-risk cardiac surgery patients. The prevalence of acute kidney injury, identified by tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 biomarkers, was reduced with the Kidney Disease Improving Global Outcomes bundle (55.1 *vs.* 71.7%; absolute risk reduction, 16.6%; 95% CI, 5.5 to 27.9%; $P = 0.004$). A Kidney Disease Improving Global Outcomes bundle enhanced hemodynamic parameters ($P < 0.05$), reduced hyperglycemia ($P < 0.001$), and ephrotoxic agent utilization of ($P < 0.001$).[192] However, the PrevAKI trial was not sufficiently powered to demonstrate a change in secondary outcomes of rate of dialysis, length of stay, and adverse kidney events with bundle implementation.[192] Current therapy has focused on minimizing the progression and optimizing the clinical response of the specific perioperative environment to improve acute kidney injury with limited success in secondary endpoints. Gocze *et al.*[193] examined urinary cell cycle arrest biomarkers, insulin-like growth factor-binding protein-7, and tissue inhibitor of metalloproteinase-2 in 107 high-risk surgical patients to predict early identification of acute kidney injury and allow for preventive measures. This rapid urinary biomarker assessment panel significantly improved

risk stratification ($P < 0.001$). Further, in combination with clinical parameters, Gocze *et al.*[193] successfully allowed for early initiation of renal protective measures (*i.e.*, hemodynamic optimization) and escalation of care before the development of acute kidney injury. Based on these studies, combinations of biomarker panels for early detection of perioperative acute kidney injury in conjunction with accelerated intervention protocols have great promise to become a cornerstone of acute kidney injury prevention in surgical patients.

Conclusions

The development of acute kidney injury has important implications for recovery and outcomes of surgical patients. Decreased urine output and an increase in serum creatinine concentrations are classically used to diagnose acute kidney injury. The search for earlier and more specific biomarkers is an area of intense research. We believe that their introduction into routine clinical praxis is eminent. A uniform classification of acute kidney injury by the Kidney Disease Improving Global Outcomes workgroup has allowed for advances in medical practice, research, and public health. Promising therapeutic advances to prevent or treat perioperative acute kidney injury continue to be a challenge. Although previous clinical trials have been disappointing, new preclinical and clinical interventions are targeting novel pathophysiology aspects of acute kidney injury inflammatory and oxidative stress response, endothelial dysfunction, microRNA modulators, and renal-specific vasodilators. Clinical research continues to explore our evolving understanding of fluid balance and type of fluid used in the resuscitation of the perioperative patient, renal replacement therapy, and alternative therapeutic approaches, such as remote ischemic preconditioning.

Advancements in risk stratification systems, with the use of instantaneous analytics, has the potential to emerge as an effective means of acute kidney injury risk assessment in the perioperative setting.[194] This combination of clinical parameters, biomarkers, and electronic medical record risk stratification will allow timely identification of subclinical acute kidney injury and initiation of renal protective measures. Once identified, a phased approach to more complex and costly evaluations can be integrated into existing low-cost and low-risk therapies.[194] The importance of rapid diagnosis cannot be overstated. It extends the opportunity for intervention, preventing the progression and development of subclinical injury to acute kidney injury. Multicenter trials and translational research are needed to further define or establish appropriate therapeutic and diagnostic opportunities in acute kidney injury. The historic premise of "do no harm" continues to be a cornerstone in acute kidney injury management, including hemodynamic monitoring approaches, fluid replacement therapy, and avoidance of nephrotoxic agents.

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Competing Interests

The authors declare no competing interests.

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