NARRATIVE REVIEW ARTICLE

Perioperative Renoprotection: Clinical Implications

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Acute kidney injury (AKI) remains a common complication in the perioperative setting affecting patients' short- and long-term outcome. Because therapeutic options are restricted to the use of renal replacement therapy, preventive strategies have become increasingly important. Several substances have been investigated for preventing AKI with limited to no effects. The lacking effectiveness of all these therapies might be caused by the fact that the therapy was started too late. In all the studies, therapy was initiated once a reduced kidney function occurred. In contrast to the classical functional biomarkers, new renal biomarkers allow to identify kidney damage without a loss of function thus enabling the implementation of preventive measures at the stage of renal stress. The most promising preventive strategy to date seems to implement a bundle of supportive measures in patients at high risk for AKI as recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) group. This strategy includes the avoidance of nephrotoxic drugs and contrast agents, avoidance of hyperglycemia, optimization of perfusion pressure and hemodynamics with consideration of a functional hemodynamic monitoring, and close monitoring of renal function in patients at high risk for AKI. This review discusses new renal biomarkers for identifying kidney damage, the background of why the different measures of the KDIGO bundle might positively affect renal function and prevent the development of AKI, and presents the current literature of biomarker-based approaches in AKI. (Anesth Analg 2020;131:1667–78)

GLOSSARY

AKI = acute kidney injury; **AKIN** = Acute Kidney Injury Network; **ASPEN** = American Society of Parenteral and Enteral Nutrition; **AUC** = area under the curve; **BaSICS** = Balanced Solution versus Saline in Intensive Care Study; **BigPAK** = Biomarker-guided intervention to prevent AKI after major surgery; **BMI** = body mass index; **CI** = confidence interval; **CKD** = chronic kidney disease; **GFR** = glomerular filtration rate; **HR** = hazard ratio; **ICU** = intensive care unit; **IGFBP** = Insulin-like growth factor-binding protein; **IL** = Interleukin; **INPRESS** = Effect of individualized vs standard blood pressure management on postoperative organ dysfunction among high-risk patients undergoing major surgery; **KDIGO** = Kidney Disease: Improving Global Outcomes; **KDOQI** = Kidney Disease Outcomes Quality Initiative; **KIM-1** = kidney injury molecule-1; **LFABP** = liver-type fatty acid-binding protein; **MAP** = mean arterial pressure; **MIMIC-III** = Medical Information Mart for Intensive Care Database; **NGAL** = neutrophil gelatinase-associated lipocalin; **NICE-SUGAR** = Intensive vs conventional glucose control in critically ill patients Trial; **NPV** = negative predictive value; **OR** = odds ratio; **PHOENICS** = Safety and efficacy of 6% hydroxyethyl starch solution vs an electrolyte solution in patients undergoing elective abdominal surgery Trial; **PLUS** = Plasma-Lyte 148 vs Saline; **PrevAKI** = Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high-risk patients identified by biomarkers; **RIFLE** = Risk, Injury, Failure, Loss, End-stage renal disease; **RRT** = renal replacement therapy; **SALT-ED** = Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department Trial; **SMART** = Isotonic Solutions and Major Adverse Renal Events Trial; **STS** = Society of Thoracic Surgery; **TETHYS** = Safety and efficacy of 6% hydroxyethyl starch solution vs an electrolyte solution in trauma patients; **TIMP** = tissue inhibitor of metalloproteinases

The occurrence of acute kidney injury (AKI) is common in the perioperative setting and remains an underestimated but clinically important complication.[1] The importance of AKI is highlighted by the fact that even milder stages of AKI are associated with adverse outcomes.[2] AKI is a syndrome that is associated with other complications including delirium,[3] infections,[4] bleeding,[5] chronic kidney disease,[6] chronic dialysis dependency,[7] cardiovascular diseases,[8] and death.[9] In view of these significant negative effects, it remains surprising that the estimated number of unreported AKI cases is very high.[10] This is due to the fact that physicians not adequately apply the functional biomarkers serum creatinine and urine output. As renal replacement therapy (RRT) is the only therapeutic option for patients with severe AKI, there is an urgent need to detect a kidney damage earlier and try to prevent AKI.

In the last decades, >35 different definitions of AKI have been used.[11] Consensus criteria namely Risk,

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Injury, Failure, Loss, End-stage renal disease (RIFLE; 2004), Acute Kidney Injury Network (AKIN; 2006), and Kidney Disease: Improving Global Outcomes (KDIGO; 2012) criteria have been developed to harmonize the different definitions and to display the broad spectrum of this clinical syndrome.[2,12] The current KDIGO definition is based on changes of serum creatinine and urine output. However, their use for early implementation of preventive measures is inappropriate because serum creatinine and urine output have a low sensitivity and specificity, respectively. These markers can only detect a functional decline of kidney function, but not an earlier isolated kidney damage. New diagnostic options have been evolved which seem promising for early diagnosing renal stress, and these may be useful for implementation of preventive strategies. As all pharmacologic options failed, the KDIGO guidelines have emphasized the implementation of a bundle to prevent AKI.[13]

The purpose of this review is to discuss new options for early diagnosis of AKI with a special emphasis on new biomarkers and their potential role in clinical routine for implementing preventive measures.

INCIDENCE AND EPIDEMIOLOGY

Approximately 2% to 18% of all hospitalized patients develop AKI during their hospital stay.[14,15] The incidence of AKI in critically ill patients is reported as high as 57%.[16] Patients who develop AKI have an increased mortality, whereas the mortality rates depends on the severity of AKI and can reach up to 60% in patients with dialysis-dependent AKI. Furthermore, health care costs and resource utilization are higher in AKI patients.[17–19]

The most common cause of AKI is sepsis, whereas the second most common cause is surgery. Patients undergoing cardiac surgery have reported AKI incidences of up to 42% based on the complexity of the surgery and the use of the cardiopulmonary bypass, including the activation of the immune and complement system, and redistribution of blood flow.[20–22] A systematic review of major abdominal surgery showed that the incidence of AKI was 13% in this patient population.[23] Additionally, patient-related risk factors for development of AKI like chronic vascular disease, chronic kidney disease, arterial hypertension, cardiac failure, and diabetes are well established and contribute to the overall risk profile.[24]

DEFINITION AND DIAGNOSIS

In 2012, the KDIGO definition was published and the definition is based on changes in serum creatinine and urine output (Table 1). Despite the improvements in standardization and practicality by accommodating absolute and relative changes in serum creatinine and allowing a short (48 hours) as well as an extended time frame (7 days) for diagnosing AKI, the main point of criticism remains due to the physiological properties and limitations of these 2 classical (functional) markers.

The functional biomarker serum creatinine has a low sensitivity. The kidney can compensate for a reduced glomerular filtration rate (GFR) by hyperfiltrating of intact glomerula. More than 50% of the GFR has to be lost before the serum creatinine levels increase. In addition, serum creatinine levels are influenced by muscle mass and dietary protein intake.[25] Recent data in an elderly Chinese population suggest that the 48-hour window seems to correlate better with mortality than the 7-day window, and sole reliance on this criterion may miss up to 30% of patients with AKI.[26] In addition, using the Cockcroft–Gault formula to estimate GFR based on serum creatinine can overestimate GFR by 16%.[27] For an accurate measurement of GFR, 24-hour urine collection is needed, which is unpractical in daily clinical practice. Furthermore, a steady state of creatinine is required, which may not be present in cases of rapid disease progression and critical illness.[28] Based on these limitations, serum creatinine does not serve well as a screening tool to allow timely initiation of any preventative measures.[29]

In contrast to serum creatinine levels, urine output has a low specificity, because this marker might be influenced by several factors including diuretics and hypovolemia. In the context of surgery, it is nearly impossible to differentiate between physiological and pathological oliguria. Surgery induces the release of antidiuretic hormone which may lead to a reduced urine output without the presence of any structural damage of the kidneys.[30] In response to hypovolemia, the antidiuretic hormone release can result theoretically in urine volumes as low as 500 mL/d (0.29 mL/kg/h for a 70-kg person), based on a daily solute load of 700 mOsmol and a maximum urinary osmolality of 1400 mOSmol/L. In the absence of hypovolemia, nonosmotic triggers of antidiuretic hormone include

Table 1. Kidney Disease: Improving Global Outcomes Criteria for Diagnosis of Acute Kidney Injury

	Serum Creatinine	Urine Output
Stage 1	Increase in serum creatinine by ≥26.5 μmol/L in ≤48 h or increase to 1.5–1.9 times from baseline within 7 days	<0.5 mL/kg/h for >6 h
Stage 2	Increase in serum creatinine 2.0–2.9 times from baseline	<0.5 mL/kg/h for >12 h
Stage 3	Increase in serum creatinine 3 times from baseline, or increase to ≥353.6 μmol/L, or treatment with RRT irrespective of the stage at the time of RRT	<0.3 mL/kg/h for ≥24 h or anuria for 12 h

Abbreviation: RRT, renal replacement therapy.

pain, stress, surgical insults, or trauma, and further antidiuretic input can originate from the sympathetic or renin–angiotensin–aldosterone system. The option to use absolute or ideal body weight for calculation complicates matters even more, especially in obese patients. The recommendations of the European Renal Best Practice Guidelines suggest to use the ideal body weight as the denominator when using the KDIGO classification.[31] Unrelated to the potential interferences of the measurement itself, the cutoff values of the urine volume for AKI are debatable as well. Some argument exists to change the KDIGO criteria for diagnosing AKI by changing the urine output threshold from 0.5 to 0.3 mL/kg/h.[32,33]

In an approach to overcome the limitations of the classical diagnostic markers for AKI, recent research has focused on identifying new AKI biomarkers.[34] These biomarkers should ideally detect kidney damage without a loss of function. The detection of this limited and potentially acute damage would allow an early initiation of renoprotective strategies.[29,35,36]

With the discovery of new biomarkers, the search for more reliable diagnostic tools with higher sensitivity and specificity intensified. The ultimate goal is to enable clinicians to identify patients at risk of AKI and predict the development of AKI in the intra- and postoperative period.

PATHOPHYSIOLOGY

The pathophysiology of AKI is complex and multifactorial. A mismatch of oxygen delivery and demand is mainly responsible for renal dysfunction. This insufficient delivery is usually due to impaired renal blood flow or impaired microcirculation. That way, hypoperfusion and inflammation are the 2 main factors for acute renal dysfunction.

Under normal circumstances, the kidneys have intrinsic (myogenic and juxtaglomerular feedback mechanisms) and extrinsic (sympathetic nervous system, renin–angiotensin–aldosterone system) autoregulatory properties. In the perioperative period, renal hypoperfusion occurs frequently through hypovolemia-associated reduction of mean arterial pressure (MAP). Initially, perfusion pressure and GFR can be maintained through the activation of the autoregulatory systems, especially the sympathetic nervous system, which results in the release of angiotensin II and antidiuretic hormone through renin. However, persistent hypoperfusion causes a decrease in GFR secondary to vasoconstriction of the afferent and efferent arterioles. The compensatory effects depend highly on the autoregulatory capabilities of the kidneys. For instance, in patients with chronic kidney disease, these mechanisms are altered.[37]

Systemic inflammation as second major factor for the development of AKI leads to tubular injury resulting in renal damage through microcirculatory dysfunction, leukocyte migration, and endothelial dysfunction.[38,39]

RISK FACTORS

Irrespective of the underlying reason for the development of AKI, a number of risk factors predispose for renal dysfunction. These risk factors include patient- and surgical-related factors.

Chronic diseases such as chronic kidney disease (CKD), diabetes mellitus, or chronic obstructive pulmonary disease are well known to be associated with the development of AKI.[40,41] In addition, obesity plays an emerging role for 2 reasons: (1) this condition is increasing worldwide and (2) it could be shown that the odds of AKI increases by 26.5% per 5 kg/m^2 body mass index (BMI).[42] Moreover, the application of nephrotoxic substances (eg, nonsteroidal anti-inflammatory drugs, aminoglycosides, vancomycin) should not be disregarded when preparing patients for surgical procedures or in the perioperative management. The consideration of comorbidities is important because these patients may have creatinine values within the normal range but decreased GFRs. In these patients, it is conceivable that less serious insults might have more detrimental effects as in patients without comorbidities.

In terms of surgery, cardiac surgical procedures with the use of cardiopulmonary bypass have the highest risk for the development of AKI. This is among others due to the tremendous effects on hemodynamics with prolonged periods of hypotension, use of vasopressors, ischemia-reperfusion injury, and inflammatory reactions. However, general, thoracic, orthopedic, vascular, and urological surgeries are further worth mentioning as an association with the development of AKI has been described. Key determinants are factors that prolong duration of intraoperative hypotension as well as the duration of renal ischemia. In abdominal surgery, 1 additional problem is abdominal hypertension affecting renal perfusion and resulting in AKI.[43]

In conclusion, the detection of patients at risk for AKI plays a pivotal role because these patients might particularly benefit from preventive strategies.

NEW RENAL BIOMARKERS

During the last decades, a growing number of new biomarkers have been studied for their suitable use in clinical practice. New markers are Cystatin-C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL18), liver-type fatty acid-binding protein (LFABP), tissue inhibitor of metalloproteinases 2 (TIMP- 2), insulin-like growth factor-binding protein 7 (IGFBP7), and endogenous ouabain. To date, most of them have not found their way into daily clinical practice. The reason

for this might be the uncertainty of how to use these damage biomarkers in clinical practice as well as the lacking possibility of measuring them at the bedside by using point-of-care devices. However, some of them will be discussed in further detail.

Cystatin-C

Cystatin-C is a low-molecular-weight protein (13.3 kDa) with protective function by inactivating endogenous cysteine proteinases which are responsible for proteolysis and tissue damage. Cystatin-C is freely filtered in the glomerulus and reabsorbed in the tubular system but does not undergo tubular secretion (in contrast to creatinine), thereby being a more reliable marker in detecting a GFR decline 1 to 2 days earlier than serum creatinine.[44] Additionally, it shows better predictive properties for death and cardiovascular events in elderly patients compared to creatinine.[45]

Cystatin-C has been shown to be superior to serum creatinine in detecting estimated GFR (via Modification of Diet in Renal Disease equation) reduction, and these findings have been confirmed in a meta-analysis.[46] It seems that Cystatin-C is less affected by body weight, age, or sex compared to serum creatinine. However, corticosteroids, hyperthyroidism, inflammation, or hypertriglyceridemia seem to influence plasma levels significantly.[47,48]

Cystatin-C is a functional marker and therefore not appropriate for early detection of renal damage. In addition, the costs and the limited availability in some regions reduces the use in clinical practice.

Neutrophil Gelatinase-Associated Lipocalin

NGAL, a 25-kDa protein, is synthesized during granulocyte maturation in the bone marrow[49] and may be induced in inflammatory processes like inflammatory bowel disease and malignancies.[50] It is also considered a marker of tubular damage.[51] Studies in pediatric and adult cardiac surgery were able to demonstrate a rise in NGAL levels 1 to 3 days earlier compared to serum creatinine increases. The predictive value of NGAL was higher in pediatric patients as compared to adults due to the higher presence of comorbidities.[52] Different comorbidities, like chronic kidney disease, alter the predictive value of NGAL, because these conditions may modulate baseline levels. After surgery, it has been shown that NGAL levels were significantly higher in patients who develop AKI.[53] A recent meta-analysis of 19 studies including over 2500 patients demonstrated the ability of serum and urinary NGAL to predict the need for RRT and overall mortality.[54] Some studies could demonstrate NGAL elevations being an independent predictor of major cardiovascular events and mortality.[55,56] One important finding resulted from a pooled analysis of prospective studies where it was demonstrated that an NGAL elevation in the absence of a serum creatinine increase was associated with an increased risk of adverse outcomes.[36] Based on these data, the term "subclinical AKI" was introduced which describes a state of kidney damage without a loss of function.[57]

However, the major drawback of NGAL is the fact that 2 isoforms exist, and available antibodies are not able to distinguish between these 2 isoforms. This means that it is impossible to differ between AKI and inflammation. It is important to know that serum NGAL levels reflect inflammation, whereas urinary NGAL levels can reflect inflammation (filtered in the glomerulus) or tubular damage.

Tissue Inhibitor of Metalloproteinases 2 and Insulin-Like Growth Factor-Binding Protein 7

TIMP-2 and IGFBP7 have been isolated among over 300 markers in a heterogeneous group of critically ill patients[58] and have shown the ability to predict the development of moderate or severe AKI within 12 hours of sample collection. Although individually each has performed better in different subgroups of patients (TIMP-2 in surgical and IGFBP7 in sepsis-induced AKI patients), they seem to have additive predictive value and multiplication of both [TIMP-2] × [IGFBP7] resulted in an improved area under the curve (AUC) of 0.80 (compared to 0.76 and 0.79, respectively). Unlike other biomarkers, [TIMP-2] × [IGFBP7] also allowed to differentiate between AKI and non-AKI conditions. Both biomarkers are expressed in early phases of cell injury resulting in G_1 cell cycle arrest.[59,60] This prevents the further replication of potentially damaged DNA. Initial smaller studies in 50 cardiac surgery patients were showing conflicting results, describing weak test performance without predictive value.[61,62] However, a single-center trial was able to identify patients at high risk of AKI by measuring urinary [TIMP-2] × [IGFBP7] levels early after cardiac surgery.[63] Later studies added to the growing body of evidence confirming the utility of [TIMP-2] × [IGFBP7] to identify at-risk patients earlier in the clinical setting.[64–66] The prospective properties of this biomarker seems to go beyond AKI. In the critically ill population, [TIMP-2] × [IGFBP7] seems to be able to identify patients at risk for developing other adverse outcomes, namely necessity of RRT or intensive care unit (ICU) mortality, independently from the development of AKI.[67,68] The use of these biomarkers may be a promising opportunity because interventions at the time point of renal damage (before loss of function) might be the window of opportunity for implementing preventive measures to prevent AKI.[58]

PREVENTIVE OPTIONS: BUNDLES

Different pharmacological options have been evaluated for the prevention of AKI without success.[69–72]

However, most of these options were applied in patients with an already reduced renal function.

The KDIGO guidelines recommend the implementation of supportive measures in patients at high risk for AKI.[13] These include the optimization of hemodynamics and perfusion pressure including the consideration of a functional hemodynamic monitoring to achieve this, the avoidance of hyperglycemia and nephrotoxic agents, consideration of alternatives to radio contrast agents, and close monitoring of renal function. How patients at high risk for AKI should be determined is not specified in the guidelines. In view of the new advances in renal biomarker research, biomarker-based strategies were evaluated for detecting patients at high risk to early implement these recommendations.

The first study using such a biomarker-based approach for implementation of the KDIGO bundle was the Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high-risk patients identified by biomarkers (PrevAKI) randomized controlled, single-center trial (Table 2).[73] Following on-pump cardiac surgery, patients were evaluated for risk of AKI by measuring [TIMP-2] × [IGFBP7] 4 hours after cardiopulmonary bypass. This strategy resulted from a previous trial, where [TIMP-2] × [IGFBP7] levels 4 hours after cardiopulmonary bypass showed best predictive performance for the occurrence of AKI thereby demonstrating patients at high risk especially those exceeding a cutoff of 0.3 $(ng/mL)^2/1000$.[63] Those patients exceeding this prespecified cutoff—and therefore at risk for AKI—were randomized to receive either a strict implementation of the KDIGO bundle (including a functional hemodynamic monitoring, optimization of volume status and perfusion pressure according to a prespecified algorithm, avoidance of nephrotoxic agents and hyperglycemia, consideration of alternatives to radiocontrast agents, close monitoring of serum creatinine and urine output, and the discontinuation of angiotensin receptor inhibitors or angiotensin receptor blockers) or standard of care. The results not only showed that [TIMP-2] × [IGFBP7] helped to identify patients at high risk but also demonstrated that the strict implementation of a bundled strategy significantly reduced the occurrence of AKI by 16.6% (95% confidence interval [CI], 5.5–27.9; $P = .004$) and the severity of AKI by 15.2% (95% CI, 4.0–26.5; $P = .009$).

Thereafter, the Biomarker-guided intervention to prevent AKI after major surgery (BigPAK) randomized controlled, single-center trial evaluated a biomarker-based bundled approach in high-risk patients undergoing major abdominal surgeries. The same biomarkers were used for identifying patients at high risk. The bundled strategy included early optimization of volume status guided by central venous pressure according to a prespecified algorithm, the discontinuation of nephrotoxic agents, and nephrology consultation if deemed necessary. The results demonstrated similar findings as in the PrevAKI cohort: a significant reduction in the incidence of all stages of AKI (27% [13/48] intervention vs 48% [24/50] control group; $P = .03$), moderate and severe AKI (6.7% [4/60] intervention vs 19.7% [12/60] standard care group; $P = .04$), and a significant shorter ICU and hospital stay.[74] However, these differences were only detectable within a specific biomarker range from 0.3 to 2.0 $(ng/mL)^2/1000$, assuming that in patients with high biomarker levels of higher than 2.0 $(ng/mL)^2/1000$, damage may be extended and AKI not preventable.

To facilitate the necessary interventions as early as possible, Ronco et al[76] proposed a dedicated rapid response team which was assigned to treating at-risk patients identified by [TIMP-2] × [IGFBP7]. In these patients, the supportive measures suggested by the KDIGO guidelines were implemented. This approach significantly reduced the incidence and severity of AKI.[76,77] These promising findings were further consolidated by a study by Engelman et al.[75] Following the routine measurement of [TIMP-2] × [IGFBP7] after cardiac surgery, a dedicated response team was activated to initiate a bundle of interventions (including targeted fluid protocol, liberalized transfusion threshold, avoidance of nephrotoxins, continuation

Table 2. Selected Studies With Biomarker-Based Approach for Renoprotection

Reference	Number of Patients	Design	Approach	Results
Meersch et al[73] (PrevAKI Trial)	276 patients undergoing cardiac surgery	Prospective, randomized, unblinded, single center	Urinary [TIMP-2] × [IGFBP7] triggering bundled care according to KDIGO guidelines	Significant reduction in incidence of AKI (KDIGO stage 2/3), no differences in secondary outcomes
Göcze et al[74] (BigPAK Trial)	125 critically ill patients after major noncardiac surgery	Prospective, randomized, unblinded, single center	Urinary [TIMP-2] × [IGFBP7] triggering bundled care according to KDIGO guidelines	Significant reduction in incidence of AKI (KDIGO stage 2/3), no differences in secondary outcomes
Engelman et al[75]	847 on-pump cardiac surgery patients	Secondary review of prospectively collected data from STS cardiac database	Dispatch of acute renal response team based on routinely measured [TIMP-2] × [IGFBP7]	Significant reduction of incidence of AKI (KDIGO stage 2/3) NPV of [TIMP-2] × [IGFBP7] = 100%

Abbreviations: AKI, acute kidney injury; BigPAK, Biomarker-guided intervention to prevent AKI after major surgery; IGFBP7, insulin-like growth factor-binding protein 7; KDIGO, Kidney Disease: Improving Global Outcomes; NPV, negative predictive value; PrevAKI, Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers; STS, Society of Thoracic Surgery; TIMP-2, tissue inhibitor of metalloproteinases 2.

of invasive monitoring and its optimization in ICU) in patients within a specific biomarker range (0.3–2.0 (ng/mL)^2/1000). The implementation of this urinary biomarkers-triggered bundle resulted in an 89% relative risk reduction of postoperative AKI stage 2/3 in cardiac surgery patients without increases in cost or length of hospital stay.

The use of a protocolized "bundled therapy" itself has already been advocated in different clinical settings to ensure comprehensive and evidence-based intervention in a timely manner. It has shown beneficial effects in treatment of sepsis[78] and in reduction of intravascular catheter-related infections and now for prevention of AKI.[79] Nonetheless, the adherence to bundles has been shown to be generally poor in different clinical settings and similar findings could recently be established for AKI.[80]

WHY BUNDLED STRATEGIES ARE USEFUL

Considering the different measures recommended by the KDIGO guidelines, it is conceivable that the adherence to a bundled approach may be effective in terms of preventing AKI.

Hemodynamic Control

One component of the proposed KDIGO bundle is hemodynamic monitoring and optimization. Intraoperative hypotension due to a change of perfusion pressure or the presence of hypovolemia can be responsible for AKI and represents a preventable risk factor.[81,82]

Common treatment thresholds in clinical practice are systolic blood pressure <80 mm Hg,[83,84] MAP <60 mm Hg,[85] or a reduction of 30% to 50% from baseline.[84] The relationship between MAP and risk for AKI seems to be proportional. A recent meta-analysis revealed that a MAP <60 mm Hg for >1 minute was associated with increased risk for AKI.[86,87] The Effect of individualized vs standard blood pressure management on postoperative organ dysfunction among high-risk patients undergoing major surgery (INPRESS) study group demonstrated that an individualized blood pressure target (within 10% of each patients resting value) was superior to the above-mentioned standard values and resulted in significant lower rates of organ dysfunction (38.1% individualized vs 51.7% standard blood pressure management; $P = .02$).[88] A recent study in noncardiac surgical patients focused on blood pressure variability and suggested that this is the value of interest.[82] They demonstrated that a higher blood pressure variability independent of hypotension was associated with higher risk of postoperative AKI.

The call for individualized goal-directed therapy raises the question of how to monitor individualized pressure goals through fluid administration. Early studies in the 1980s started with looking at goal-directed therapies utilizing pulmonary artery catheters.[89,90] These were followed by esophageal Doppler sonography[91] and more recently by calibrated pulse contour analysis.[92] The use of functional parameter for guidance of fluid management has been under some criticism, because of the increased risk of hypervolemia. A recent meta-analysis looked at uncalibrated pulse contour analysis for monitoring and demonstrated that goal-directed therapy resulted in more colloid administration but less crystalloid solutions without a change in total fluid amount.[93]

In terms of fluid administration, multiple studies noted the large variability of intraoperative application of fluid volume.[94,95] Evidence suggests that a treatment of hypovolemia should not result in fluid overload because fluid overload is associated with the occurrence of AKI and less recovery from AKI.[96–98] Based on data from patients undergoing major abdominal surgery, some studies advocated a more restrictive fluid management and demonstrated that this approach led to a reduced postoperative complication rate and shorter length of hospital stay.[99,100] These findings resulted in international consensus statements supporting restrictive fluid management to facilitate enhanced recovery after surgery.[101,102] However, on the other hand, a growing body of evidence suggests that this strategy not only worsens respiratory function but also increases the risk for wound healing and sepsis.[103] Of special concern is the impact of hypovolemia on AKI due to impaired renal autoregulatory abilities, facilitating further renal injury and worsening AKI.[104,105]

Apart from the amount of fluid, the type of fluid that is given remains a matter of ongoing debate. Current evidence suggests the use of balanced crystalloid instead of chloride-rich solutions. The rationale behind this is that chloride-rich solutions cause renal vasoconstriction and have been shown to deteriorate kidney function.[106,107] Two large trials were recently published: the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) and Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial, 2 cluster-randomized, cluster-crossover trial comparing balanced crystalloid with 0.9% sodium chloride for patients in the ICU and emergency department.[108–110] Both trials demonstrated that especially patients at high risk are at risk for the development of major adverse kidney events consisting of persistent renal dysfunction, need for RRT, or mortality after 30 days: SMART: 14.3% vs 15.4%; odds ratio (OR), 0.90; 95% CI, 0.82–0.999; $P = .04$) and SALT-ED: 4.7% balanced crystalloid vs 5.7% saline group; OR, 0.82; 95% CI, 0.70–0.95; $P = .01$). Two trials, the Plasma-Lyte 148 vs Saline (PLUS) and Balanced Solution versus Saline in Intensive Care Study (BaSICS) trials, are ongoing which may provide

more insights into the effects of saline solutions on outcomes in critically ill adults. However, high doses of saline solutions should not be used in the critical care setting.

This also applies to the administration of hydroxyethyl starch because there is overwhelming evidence that starch solution may foster the occurrence of AKI in vulnerable patients[111,112] as well as mortality in critically ill patients with sepsis.[113–115] There are currently recommendations against the use of starch in septic and burned patients as well as a boxed warning by the Food and Drug Administration.[116] However, new preparations of hydroxyethyl starch solutions (130/0.4) are currently being investigated in 2 international prospective, multicenter, randomized controlled trials (Safety and efficacy of 6% hydroxyethyl starch solution vs an electrolyte solution in patients undergoing elective abdominal surgery [PHOENICS], NCT03278548, and Safety and efficacy of 6% hydroxyethyl starch solution vs an electrolyte solution in trauma patients [TETHYS], NCT03338218). Whether the results revoke some of the apprehension around hydroxyethyl starch remains to be awaited.

In summary, the assurance of an adequate perfusion pressure and volume status is an important mainstay of the KDIGO bundle and has a tremendous effect on the occurrence of AKI. Paying attention to avoid excessive hypovolemia as well as hypervolemia, using preferentially buffered isotonic crystalloid solutions for expansion of intravascular volume assisted by use of vasopressors to an individual blood pressure target are the main tasks of the attending physicians.

Glycemic Control

Different groups have investigated glycemic control in critically ill patients in terms of AKI and suggested a clear relationship between poor glycemic control and worse outcomes (Table 3).[13,31,117–121]

The management of blood glucose levels seems to follow a U-shaped relationship. Van den Berghe et al[122,123] were able to demonstrate a reduction of mortality and lower rates of RRT when using tight glycemic control. However, the Intensive vs conventional glucose control in critically ill patients (NICE-SUGAR) group demonstrated that a too tight glycemic control also increases the risk of hypoglycemia and death.[124] This needs to be kept in mind for the following reason: glycemic hemostasis is impaired in kidney injury patients. The kidneys are responsible for 50% of insulin clearance, and they contribute to around 30% of the overall gluconeogenesis.[125,126] This might be a reason why patients with AKI are more susceptible to the development of hypoglycemia when treated for hyperglycemia.

Nevertheless, the topic of blood sugar control remains a highly debated topic, and the degree of glycemic control might need to be adjusted for the individual patient population.[127] Similar to recent observations of blood pressure variability, some evidence suggests that not the absolute blood sugar level per se results in AKI, but the variability.[128] At this stage, it remains unclear if hyperglycemia, insulin resistance, and the variability are true contributors of poor outcome or if they are just an indicator for general metabolic derangement. Currently, the KDIGO guidelines suggest to adhere blood glucose levels between 110 and 149 mg/dL to prevent the occurrence of AKI.

Table 3. Guidelines on Glycemic Control

Guidelines	Patients	Glycemic Control Range
Surviving Sepsis Campaign[120]	Critically ill patients with sepsis	<180 mg/dL
American Diabetes Association[119]	Critically ill patients	144–180 mg/dL
ASPEN[118]	Critically ill patients	140–180 mg/dL
KDIGO[13]	AKI in the ICU	110–149 mg/dL
European Best Practice Guidelines[31]	AKI in the ICU	110–180 mg/dL
KDOQI on KDIGO 2012[117]	AKI in the ICU	110–149 mg/dL

Abbreviations: AKI, acute kidney injury; ASPEN, American Society of Parenteral and Enteral Nutrition; ICU, intensive care unit, KDIGO, Kidney Disease Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative.

Nephrotoxic Agents

Diuretics. The question whether to use diuretics for prevention of AKI arises repeatedly. The KDIGO guidelines clearly recommend that the use of diuretics should be reserved for regulation of fluid balance and not as a preventative tool to avoid AKI.

The theoretical mechanism of furosemide for preventing AKI includes decreasing GFR and tubular workload resulting in less renal medullary metabolic demand as well as acting as a vasodilator.[129] However, this remains controversial. Lassnigg et al[130] compared the administration of isotonic sodium chloride, continuous infusion of dopamine (2 µg/kg/min, "renal dose") ,or furosemide (0.5 µk/kg/min) in a cohort of elective cardiac surgical patients in terms of reduction of postoperative creatinine levels. They found highest increase in creatinine levels in patients receiving furosemide assuming that furosemide is even detrimental in terms of prevention of AKI. A further trial among high-risk patients undergoing cardiac surgery demonstrated that patients receiving furosemide (4 mg/kg until 12 hours after surgery) had the same incidence of renal dysfunction as compared to those patients receiving saline solution as placebo.[131] In a meta-analysis utilizing the Medical Information Mart for Intensive Care (MIMIC-III) database,[132] furosemide administration was associated with reduced in-hospital mortality (hazard ratio [HR], 0.67; 95% CI, 0.61–0.74; $P < .001$) and 90-day mortality (HR, 0.69; 95% CI, 0.64–0.75; $P < .001$).[133] Of note, these findings were only valid for

moderate and severe AKI based on urine output and not based on serum creatinine or chronic disease.

In certain situations (contrast medium administration), loop diuretics may act protectively but only if intravascular volume and consequently renal perfusion pressure is maintained.[134] Whether these findings can be verified in large, prospective, randomized controlled trials remains to be seen. Based on current evidence, diuretics for prevention of AKI cannot be recommended.

Contrast Agents. There is a growing body of evidence questioning whether the concerns regarding contrast-induced AKI are justified. Neither a meta-analysis from 2013[135] nor a more recent meta-analysis from 2018 including 28 studies and 107,335 patients receiving contrast-enhanced computed tomography could demonstrate a significant increase in AKI.[136] These findings remained valid even when controlled for type of contrast agent or comorbidities. Furthermore, a secondary analysis from 2020 confirmed similar findings.[137] No association between preoperative contrast administration and AKI within 48 hours after gastrointestinal or hepatobiliary surgery could be demonstrated. There may be 2 possible reasons for these findings: (1) new contrast agents are less nephrotoxic and (2) the dose makes the poison. The KDIGO guidelines recommend to avoid contrast agents if possible and this is what should be considered in daily clinical practice.

CONCLUSIONS

AKI is still an underrecognized but severe clinical condition and needs to be focused on in daily clinical practice to reduce adverse outcomes. The pathophysiology is complex, and its prevention requires an individualized approach. At this stage, preemptive implementation of bundled interventions, guided by urinary biomarkers, seems the most promising strategy. The early detection of AKI with the use of new renal stress markers is gaining more importance. Hemodynamic optimization, adequate fluid therapy to maintain organ perfusion, and avoiding hyperglycemia play a pivotal role, and attention to these issues as well as risk–benefit assessment of nephrotoxic substances should be considered in daily clinical practice. Individualized thresholds according to the patients underlying comorbidities and condition instead of absolute values seem to be the true path to prevent AKI. Diuretics cannot be recommended but may be considered for prevention of fluid overload. The next challenge will be to evaluate pharmacologic options using biomarker-based approaches to find further preventive options and to continue the search for actual treatment modalities to aid repair of renal tissue. ■

DISCLOSURES

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Name: Alexander Zarbock, MD.
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