

Case Scenario: Hemodynamic Management of Postoperative Acute Kidney Injury

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ACUTE kidney injury (AKI) is associated with poor outcome both in critically ill patients and after major surgery.¹ The occurrence of AKI has been associated with poor short-term and long-term outcome, increased risk of chronic renal failure, and increased risk of death.² Several risk factors of postoperative AKI have been identified, and may help identifying patients with the highest risk of AKI. However, recognizing contributors to AKI (*e.g.*, systemic inflammation, systemic hemodynamics alterations, nephrotoxic agents, and others) remains a challenge for anesthesiologists and intensivists because these factors are often associated and AKI multifactorial.

The early diagnosis of AKI remains another issue. Interest in the development and validation of AKI biomarkers has increased among the medical community. In this article, we analyze the risk factors of and contributors to AKI after major surgery, and specifically discuss the strategy of fluid management and potential negative outcome associated with inappropriate fluid administration, with a case scenario intended to illustrate the current knowledge of perioperative

AKI. We emphasize hemodynamic management for the prevention and correction of acute renal failure.

Case Report

A 59-yr-old woman with a history of diabetes and hypertension underwent abdominal surgery for recurrent ovarian cancer. She had received systemic chemotherapy during the 18 months preceding the surgery, including paclitaxel, carboplatin, bevacizumab, doxorubicin, and cyclophosphamide, and had remained asymptomatic since then. The surgery included an ovarian resection and peritoneal carcinosis cytoreduction. The only preoperative medication was an angiotensin-converting enzyme inhibitor to treat arterial hypertension. The preoperative creatinine clearance was estimated at 80 ml/min (Modification of Diet in Renal Disease formula). Because she was asymptomatic (no dyspnea or recent change in her clinical status), left ventricular function was not preoperatively assessed.

The known large fluid losses associated with peritoneal carcinosis cytoreduction, intraoperative oliguria, and hypotension led to the infusion of a total of 24 ml·kg⁻¹·h⁻¹ of crystalloids during the 9-h surgery (half saline and half Ringer's lactate solutions). Perioperative maintenance of mean arterial pressure at 70 mmHg was achieved by intravenous infusion of neosynephrine (0.35 µg·kg⁻¹·min⁻¹). In the recovery room, cold extremities and discrete knee mottles were noted, which motivated a switch to norepinephrine infusion (0.2–0.3 µg·kg⁻¹·min⁻¹). Because of oliguria during the surgical procedure and anuria in the immediate postoperative period, with urine output less than 0.5 ml·kg⁻¹·h⁻¹, the patient was transferred to the postoperative intensive care unit (ICU). Blood analysis showed a metabolic acidosis, with a chloride concentration of 114 mM and bicarbonates of 12 mM, with a normal anion gap (14 mM). Serum alanine aminotransferase and alanine transaminase were increased (245 and 257 U, respectively), and serum troponin T was 0.223 µg/l. ICU-admission urine level of neutrophil gelatinase-associated lipocalin was 353 ng/mmol urine creatinine. Serum cystatin C was 1 mg/l,

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urine -1 microglobulin was 90 mg/l, and the fractional excretion of urea was 29%.

At admission, central venous pressure (CVP) was measured at 24 mmHg, with central venous oxygen saturation (ScvO₂) at 66%. Transthoracic echocardiography revealed a severe left ventricular dysfunction, with an ejection fraction of 25%, global hypokinesia, right ventricular dilation, systolic pulmonary arterial pressure at 30 mmHg, and low cardiac output (2 l/min). The serum level of brain natriuretic peptide was 1244 ng/ml.

Norepinephrine was switched to epinephrine, which led to an increase in cardiac output to 4.5 l/min and ScvO₂ to 88% and a CVP decrease to 15 mmHg. Intravenous infusion of furosemide was initiated, which increased urine output. AKI was reversed within 72 h and epinephrine was stopped 24 h later. The patient was discharged from the ICU after 5 days. Serum creatinine at hospital discharge was 60 µm. A cardiac magnetic resonance imaging performed 2 months later showed global hypokinesia (left ventricular ejection fraction 21%) with no sign of hypoperfusion. The final diagnosis was acute decompensated heart failure due to chemotherapy toxicity after major abdominal surgery complicated by AKI.

Discussion

Can Preoperative Patients Who Have a High Risk of Postoperative AKI Be Detected?

AKI affects 1–30% of patients after surgery. This case scenario raises the question of the preoperative evaluation of the risk of postoperative AKI. Several risk factors have been associated with postoperative AKI.

Cardiac Surgery Patients

Cardiovascular surgery is by far the highest risk procedure associated with postoperative AKI, with up to 30% of patients experiencing AKI. In comparison, the prevalence of AKI after major noncardiac surgery procedures¹ such as in the presented case, is approximately 1%. The preoperative estimation of the risk of postoperative AKI by an anesthesiologist relies on checking the risk factors of AKI. Most of the risk factors are nonmodifiable because they are procedure-related (urgent surgery, need for surgical reexploration, and cardiopulmonary bypass duration) or patient-related (age >70 yr, diabetes, atrial fibrillation, left ventricular dysfunction, preoperative intraaortic balloon pump, or chronic renal insufficiency). Preoperative evaluation (*e.g.*, with echocardiography) of left and right ventricular functions is recommended in patients with a dyspnea of unknown origin or worsening dyspnea with a known cardiomyopathy.³ In addition, Karkouti *et al.*⁴ identified a per-cardiopulmonary bypass hematocrit of less than 20% and erythrocyte transfusion as potential modifiable risk factors for postoperative AKI. These findings are in line with experimental data showing the impact of normovolemic hemodilution promoting renal hypoxia.⁵

However, perioperative erythrocyte transfusion was associated with an increased risk of AKI. The negative impact of erythrocyte transfusion supports the poor tolerance of multiple morphological and functional changes induced by erythrocyte storage (less deformability, depletion of 2, 3-diphosphoglycerate, inflammation, and decrease of bioavailability of nitric oxide with the liberation of free hemoglobin). These storage-induced modifications may induce a poor restoration of microcirculatory oxygenation associated with inflammation and changes in immune status. These observations emphasize the need for strategies that limit perioperative anemia and transfusion.⁶

The presence of proteinuria in the preoperative period, which is easily detected by dipsticks, can indicate a risk of AKI. Mild (trace to 1+) or heavy (2+ to 4+) proteinuria has been associated with increased odds of the postoperative need for renal replacement therapy (odds ratio 7.29; 95% CI, 3.00–17.73) and mortality after cardiac surgery (hazard ratio: 1.88 for mild and 2.28 for heavy proteinuria).⁷

Noncardiac Surgery Patients

In a large monocentric prospective study, Kheterpal *et al.*¹ identified age, emergent surgery, liver disease, high body mass index, high-risk surgery (*i.e.*, surgeries with the potential for large fluid shifts or blood loss), peripheral vascular occlusive disease, and chronic obstructive pulmonary disease as independent preoperative risk factors for postoperative AKI after major noncardiac surgery in patients with previously normal renal function (defined as creatinine clearance >80 ml/min). The authors created a predictive model of postoperative AKI with reasonable sensitivity and specificity but insufficient predictive values for a single patient-centered prediction. Finally, patients with poor preoperative physiological conditions, estimated by the classification of the American Society of Anesthesiologists as class IV or V, were found to be at high risk for AKI.⁸ In our case scenario, three risk factors were present: age, hypertension, and intraperitoneal surgery with large fluid losses.

Diagnosis of AKI

AKI is defined by a decrease of glomerular filtration rate (GFR). AKI is defined under the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE), the acute kidney injury network (AKIN), or the kidney disease improving global outcome (KDIGO) classification⁹ as an increase in serum creatinine level and decrease in urine output. The use of GFR estimation by Cockcroft–Gault or the Modification of Diet in Renal Disease formulae should be restrained to preoperative evaluation of GFR when renal function is stable because these formulae yield substantial disagreements regarding creatinine in patients with AKI. However, anesthesiologists must be aware of two important factors while interpreting serum creatinine levels. First, it takes time for serum creatinine to reach a steady state after a fall in GFR because of its large volume of distribution (~60% of total

body weight). It is therefore difficult to predict the course of AKI when serum creatinine increases (in other words, when the plateau of GFR is reached). Second, fluid loading and hemodilution may underestimate the increase in serum creatinine levels. Macedo *et al.*¹⁰ described a simple formula to correct serum creatinine for fluid balance and overcome this limitation (adjusted creatinine = serum creatinine \times correction factor with correction factor = (hospital admission weight [kg]) \times 0.6 + Σ (daily cumulative fluid balance [l])/hospital admission weight \times 0.6). In the present case scenario, the correction of serum creatinine with respect to fluid overload allows reclassification as stage 1 AKI according to the AKIN classification in the immediate postoperative period, with earlier diagnoses. The baseline serum creatinine was 69 μM and increased postoperatively to 77 μM . This value became 94 μM after adjustment on cumulative fluid balance, which corresponds with stage 1 AKI.

Can Postoperative AKI Be Prevented?

Successfully preventing AKI requires the correction of factors that contribute to AKI in the perioperative period, presented in figure 1.

What Is the Contribution of Hypoperfusion to Postoperative AKI?

Although profound and prolonged interruption of renal blood flow leads to oxygen debt, renal ischemia, and tubular necrosis,¹¹ the total interruption of renal blood flow is a rare clinical scenario. Suprarenal aortic clamping, renal transplantation, renal artery thrombosis or dissection, and prolonged cardiac arrest can cause renal ischemia with parenchymal injury, including some degree of tubular necrosis. Intraoperative hypotension has been statistically associated with AKI only in patients with preoperative multiple risk factors for AKI.¹² Renal blood flow and GFR decrease with a decrease in mean arterial pressure below the lower autoregulation threshold for renal blood flow and glomerular filtration. If targeting a mean arterial pressure above 65 mmHg is not necessary for preventing the development of AKI in ICU patients with preserved autoregulation of GFR, an increase in mean arterial pressure may be necessary in other cases with impaired glomerular filtration autoregulation, such as that observed in advanced age, atherosclerosis, chronic hypertension, or diabetes. Ischemic injuries and inflammatory states, cardiopulmonary bypass, and oxidative stress are

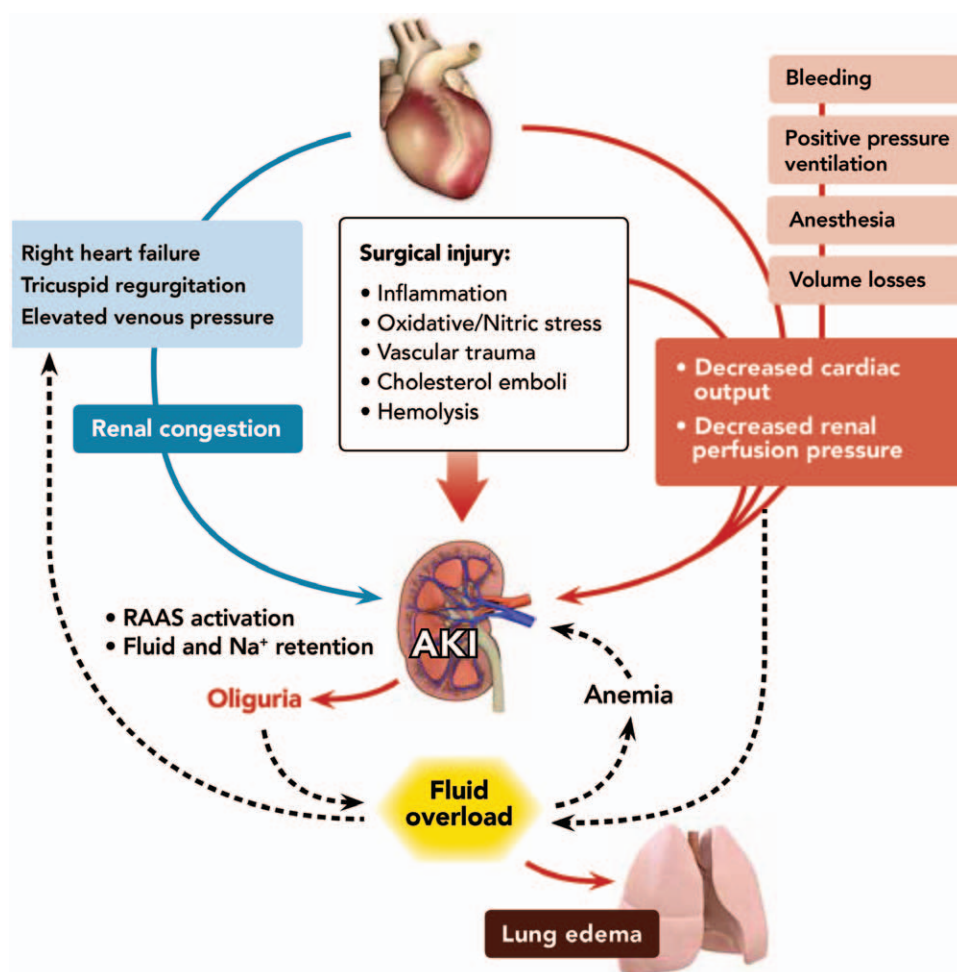


Fig. 1. Schematic representation of factors contributing to the development of acute kidney injury (AKI) in the perioperative period and the risk associated with fluid overload. RAAS = renin-angiotensin-aldosterone system.

conditions prone to affect renal blood flow autoregulation. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers impair glomerular filtration autoregulation but do not impair renal blood flow autoregulation.

The so-called “prerenal azotemia” (*i.e.*, with renal structural integrity) is often associated with tubular injury and might be considered a milder form of AKI on a continuum that includes more severe forms of AKI. The rapid reversibility of AKI with low sodium excretion is not sufficient to make the diagnosis of pure prerenal azotemia because transient AKI is associated with the increase of some biomarkers of renal damage.¹³ Furthermore, persistent AKI cannot be designated as “acute tubular necrosis.” Kidney biopsies in the immediate postmortem period of septic shock rarely identified tubular necrosis but often identified infiltration by inflammatory cells and cellular apoptosis with vascular microthrombosis.¹⁴ Consequently, the term “acute tubular necrosis” as it is classically used to describe a persistent AKI in an acute state seems inappropriate when histologic analysis of kidney has not been performed.

Perioperative Hemodynamic Optimization: A Goal-directed Therapy

Fluid resuscitation is central in the prevention and treatment of AKI. Futier *et al.*¹⁵ observed a higher incidence of postoperative complications (*e.g.*, anastomotic leak and sepsis) and lower urine output in the restrictive group compared with the liberal group, after abdominal surgery. This postoperative complication might arise in patients with a higher incidence of hypovolemia (defined as pulse pressure variation of 13% or more) and lower ScvO₂ in the restrictive group because both are independently associated with postoperative complications. Unfortunately, anesthesiologists were blinded to ScvO₂, an important variable to guide fluid resuscitation, and no clear mechanistic relation can be mentioned. Fasting has furthermore been shown to blunt renal blood flow autoregulation in rats. In contrast, there is also evidence from preclinical and clinical studies indicating that excessive fluid-administration strategies can induce the development of organ failure.¹⁶ Excessive fluid resuscitation can induce transient hemodilution by increasing renal oxygen consumption while decreasing renal oxygen transport and leads to renal hypoxia. Such a decrease of renal parenchyma oxygen bioavailability may further compromise tissue oxygenation in conditions of potential renal injury.⁵ In the worst scenario, fluid loading can worsen renal injury function due to renal congestion and increased intracapsular pressure. Therefore, more than the total amount of fluid administered is tailored and based on a perioperative stroke volume optimization, which may better prevent postoperative AKI. A recent review of randomized controlled trials¹⁷ reported that fluid resuscitation based on goal-directed therapy resulted in fewer postoperative AKIs, but any additional administered fluid was limited (median: 555 ml). The decrease in AKI was greatest in the 10 studies

in which fluid resuscitation was the same between the goal-directed therapy and control groups. More importantly, inotropic drug use in goal-directed therapy patients was associated with decreased AKI, whereas studies not involving inotropic drugs found no effect. The greatest protection from AKI occurred in patients with no difference in total fluid delivery or use of inotropes. These and other results suggest that goal-directed therapy aiming to increase flow with volume, inotrope, or a combination might be the protective factor. This treatment has been formalized in multifaceted protocols for decision-making processes to administer fluids, inotropes, and erythrocyte transfusion. Although goals differed among studies, targeting a cardiac index more than 2.5 lmin⁻¹ m⁻², a central venous oxygen saturation (ScvO₂) of more than 70%, and/or an oxygen delivery index of more than 600 mlmin⁻¹ m⁻² appears to be a sound approach. In the present scenario, the intraoperative monitoring of cardiac output and ScvO₂ would have indicated a need for inotropic support and not pure vasopressive therapy (*i.e.*, neosynephrine).

Some differences between inotropes might be observed. For example, the use of dopexamine appears to efficiently improve organ blood flow and prevent an episode of AKI, whereas the infusion of dopamine did not.¹⁸ The consequences of using vasopressor drugs on renal blood flow and renal function remain under debate because the renal hemodynamic consequences may depend on the inflammatory context. High doses of nonphysiological norepinephrine in healthy animals decreased renal blood flow and promoted renal ischemic injury.¹⁹ However, during vasodilatory shock, the infusion of norepinephrine could restore renal perfusion pressure and increase renal conductance and renal blood flow.²⁰ Derudder *et al.*²¹ observed a decrease in the renal resistive index, likely reflecting a decrease of renal vascular resistance in septic patients when blood mean arterial pressure increased from 65 to 75 mmHg with the use of norepinephrine. Similarly, Redfors *et al.*²² found that increasing blood mean arterial pressure with norepinephrine increased renal blood flow and the GFR after cardiac surgery. In a recent study we found no association between norepinephrine infusion for septic shock treatment and incidence/severity of AKI.²³ Finally, it is worth mentioning that no strategy other than hemodynamic optimization has proven to protect kidney function in patients undergoing surgery.²⁴

How Should Fluid Administration with Urine Output Be Guided in the Perioperative Setting?

Urine output is often used to guide fluid therapy in the perioperative setting, and oliguria is considered a marker of hypovolemia. However, a transient decrease in urine output is not necessarily associated with a decrease in the GFR but may result from a normal renal adaptation to maintain homeostasis. The risk of fluid overload may occur if oliguria reflects surgical- and anesthesia-related neurohormonal

adaptation with modest hypovolemia. An increase in intraabdominal pressure during laparoscopic surgery, mechanical ventilation with positive end-expiratory pressure, and pain and surgical stress with release of an antidiuretic hormone are all factors inducing antidiuresis.²⁵ Even a minor surgical injury can impair renal fluid elimination after fluid loading.²⁶ In a randomized controlled trial, urine output and postoperative creatinine serum concentration were not affected in obese patients undergoing laparoscopic surgery, who were randomly assigned to intraoperatively receive high ($10 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$; $n = 55$) or low ($4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$; $n = 52$) volumes of Ringer's lactate.²⁷ Finally, Holte *et al.*²⁸ did not observe signs of lower plasma volume when infusing 15 ml/kg compared with 40 ml/kg of Ringer's lactate over 1.5 h during laparoscopic cholecystectomy.

The clinical context and risk assessment of AKI appear central in the therapeutic response to oliguria in a patient. Oliguria in a patient undergoing surgery for a bowel obstruction or hemorrhage indicates associated hypovolemia requiring fluid infusion. Fluid deficit is also easily identified in patients with preoperative diarrhea or dehydration due to diuretics. Tachycardia, low mean arterial pressure, encephalopathy, capillary refill time, mottles, and cold extremities are important clinical signs of hypoperfusion, indicating the initiation of fluid resuscitation. However, resuscitation should be rapidly guided by physiological endpoints obtained by monitoring the optimization of cardiac output and central venous saturation (fig. 2) during the perioperative period if oliguria persists despite initial fluid resuscitation ($500\text{--}1000 \text{ ml}$ of crystalloids).

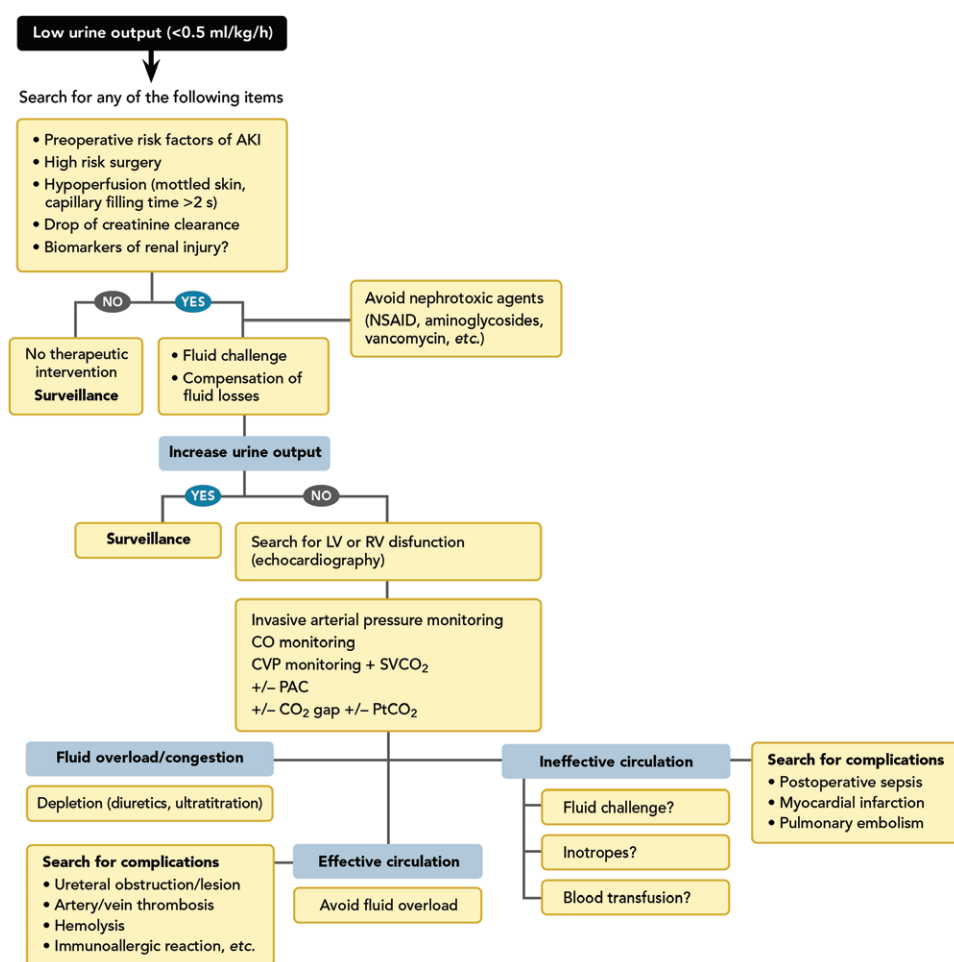


Fig. 2. Proposed strategy algorithm for treatment of oliguria in the postoperative period. Left and right ventricular function should be assessed, with estimation of cardiac output and signs of congestion. Functional hemodynamic monitoring provides guidance for resuscitation with vasopressors, inotropes, fluid or blood transfusion. When no sign of ineffective circulation (e.g., cardiac index $>2.5 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, central venous oxygen saturation– $\text{ScvO}_2 >75\%$, no clinical sign of hypoperfusion, and others) and/or presence of acute lung injury can be identified, a restrictive fluid strategy should be preferred. Depletion should be considered in case of renal congestion including high central venous pressure (CVP) \pm right heart failure, tricuspid regurgitation, and dilated inferior vena cava. Finally, titration of norepinephrine based on interlobar arteries on renal Doppler has been proposed for a tailored adjustment of renal perfusion pressure. AKI = acute kidney injury; LV = left ventricle; RV = right ventricle; NSAID = nonsteroidal antiinflammatory drug; CO = cardiac output; PAC = pulmonary artery catheter.

Avoid Fluid Overload and Venous Congestion in the Postoperative Period

A role of renal venous congestion in renal injury has emerged in experimental studies. In patients with acute heart failure, increased CVP was found to be associated with the progression of AKI, whereas cardiac output did not show this association.²⁹ Damman *et al.*³⁰ also found that increased CVP was associated with a reduced GFR. Interestingly, the negative impact of increased CVP is additive to compromised renal blood flow due to low cardiac output.³⁰ In acute lung injury, a restrictive fluid-administration strategy for surgical patients (CVP ≤ 4 mmHg and pulmonary artery occlusion pressure ≤ 8 mmHg) in the absence of shock and oliguria with a cardiac index of more than $2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ resulted in more ventilator- and ICU-free days compared with a liberal strategy,³¹ but was not associated with more episodes of severe AKI.

A relationship between fluid overload and mortality in critically ill patients was recently reported. The recent *post hoc* analysis of the Vasopressin in Septic Shock Trial study reported that a positive fluid balance and increased CVP were associated with increased risk of death in patients with septic shock.³² However, the survival rate improved when the fluid balance was positive in patients with a CVP of less than 8 mmHg, suggesting that only excessive fluid restriction may be deleterious. In a randomized control trial of critically ill patients, achieving supranormal values for the cardiac index or normal values for mixed venous oxygen saturation did not reduce the incidence of acute renal failure or reduce morbidity or mortality among critically ill patients.³³

These observational studies highlight the importance of CVP monitoring in patients with heart failure or hemodynamic instability, who are undergoing major surgery. Observing the response of CVP to a fluid challenge is important because it provides information on the reach of the limit of cardiac compliance, which leads to the potential halting of fluid administration to avoid the risk of venous congestion and further organ damage.³⁴

Which Fluid Solution Should Be Used for the Kidney?

Crystalloids. A more physiologic chloride concentration provides the advantage of balanced solutions (Ringer's lactate or acetate or Hartmann solution) over normal saline. Although normal saline is the solution of choice in hypochloremic states (*i.e.*, vomiting, gastric drainage, and treatment with diuretics), normal saline induces hyperchloremic acidosis in patients with normal initial serum chloride concentrations in the perioperative setting. Experimental and clinical data show that increased plasma chloride concentration increases renal vascular resistance and decreases renal blood flow and a reduced GFR. This strategy to reduce chloride-containing solutions appears to prevent episodes of AKI in ICU patients.³⁵

Hydroxyethyl Starches Are Associated with Negative Outcome. The fluid resuscitation of brain-dead organ donors, based on hydroxyethyl starches (HES), is associated with

an increased risk of AKI in kidney transplantations. In another randomized controlled trial, Schortgen *et al.*³⁶ found that septic patients treated with HES 200/0.6 showed a higher incidence of AKI compared with patients treated with gelatins. The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study showed a higher incidence of AKI in septic patients treated with HES 200/0.5 compared with those treated by crystalloids. Developed HES with lower molecular weight (130 kd) have been proposed because of the expected better risk/benefit ratio. The recently published 6S and Crystalloid *versus* Hydroxyethyl Starch trials did not confirm these expectations because the risk of AKI persisted with smaller molecular weight HES (HES 130/0.4), which induced a higher rate of mortality and/or dialysis.^{37,38} Together, these trial data indicate an increased risk of AKI when HES are used. Precautions can be extended to other conditions, especially with the presence of acute inflammation (*e.g.*, burns, cardiopulmonary bypass, postcardiac arrest syndrome). The safety profile of HES remains matter of debate during surgery.³⁹ Gelatins appear to have a safer profile, but there is little evidence for the potential risk of AKI. Finally, extra physiologic plasma oncotic pressure after the administration of a large amount of hyperoncotic solutions can decrease the GFR.

Use of Biomarkers

Urine biochemistry is frequently used to diagnose prerenal azotemia and guide fluid administration in the perioperative setting and in ICU patients, suggesting that the given parameters are indicators of renal tissue integrity and preserved tubular function. Recent evidence has suggested that urine chemistry is not a reliable tool for predicting the rapid reversibility of AKI. Preserved renal tubular sodium or urea handling does not necessarily indicate an absence of renal injury. Recently, Nejat *et al.*¹³ found that patients with suspected prerenal azotemia showed evidence of structural injury, with increased biomarkers of renal injury. However, increased sodium excretion does not indicate tubular necrosis. Inflammation mediators have been shown to induce tubular cell dysfunction with conformational changes of the tubule Na⁺/H⁺ exchanger, urea, or chloride channels, which influence urine composition independent of any structural damage.^{13,40} Biomarkers of renal injury (*i.e.*, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1) are expected to be used in diagnosis of tubular damage.⁴¹ Many uncertainties remain regarding their validity at the bedside. The most promising biomarkers for renal injury appear to be the neutrophil gelatinase-associated lipocalin and kidney injury molecule-1. As an example, mild renal structure damage can lead to the profound loss of glomerular and/or tubular function in a patient with underlying structural alteration (*e.g.*, chronic hypertension, diabetes); however, the same injury will not alter the function of an intact kidney (fig. 3). A combination

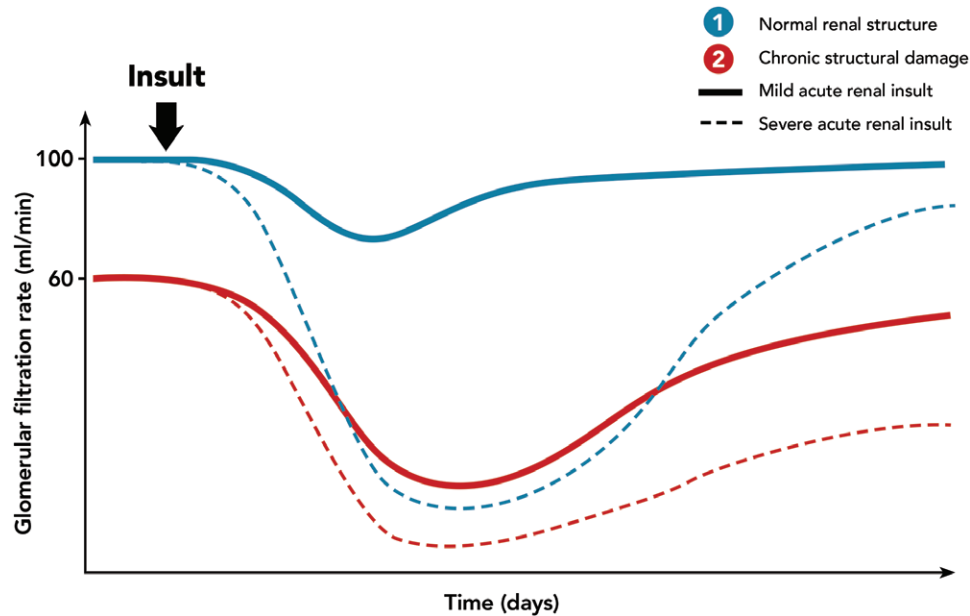


Fig. 3. Graphic representation of the respective contribution of chronic renal damage (comorbidities) and acute injury in the development of acute kidney injury (AKI) and the fall of glomerular filtration rate (GFR). An acute insult will lead to profound renal injury and definitive loss of function in the kidney with chronic renal damage (e.g., diabetes, hypertension, mild chronic renal dysfunction) while only transiently and mildly decreasing GFR in healthy kidney. Urine and/or serum level of renal injury biomarkers may help to assess the degree of structural injury to the kidney. Note that renal function may not fully recover.

of biomarkers of structural injury may therefore provide a more accurate picture of renal injury compared with a single-biomarker approach.

Knowledge Gap

The optimization of systemic hemodynamics is believed to increase renal perfusion. However, the true contribution of renal hypoperfusion to the development of AKI, especially in severe sepsis and septic shock, remains a matter of debate. Intrarenal microcirculatory defects, regional and systemic

inflammatory cell infiltration, and apoptosis are believed to be central in the development of AKI. Although a correlation between cardiac output and renal blood flow has been described in patients with AKI, the relationship among cardiac output, renal blood flow, renal injury, and renal function remains poorly explored. Although the development of new biomarkers of renal injury may allow the assessment of renal structure damage, tools to reliably assess renal perfusion and rapid changes in renal perfusion in patients at the bedside remain lacking. Renal Doppler of renal interlobar

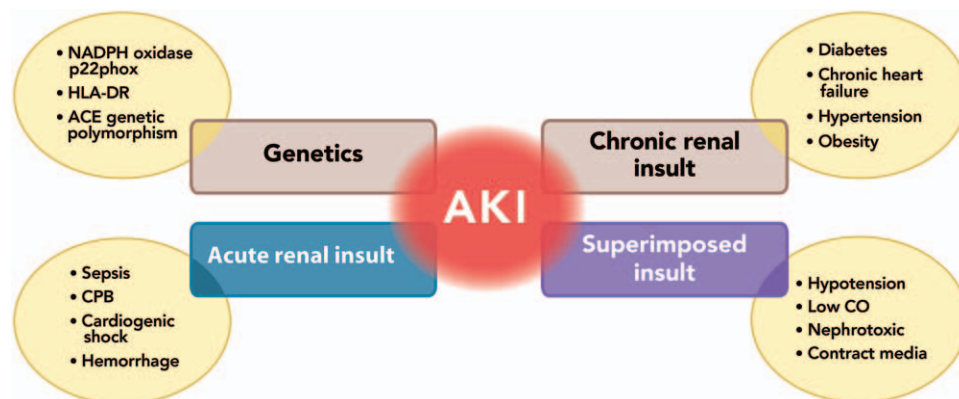


Fig. 4. Contributing factors of acute kidney injury (AKI). Note that the respective contribution of each may vary. For instance, an episode of septic AKI is mainly related to the systemic and regional inflammatory response to infection causing microvascular disorders, apoptosis, necrosis. However, a superimposed nephrotoxic agent or severe hypoperfusion can lead to further damage and/or impaired recovery. Future research should help in the understanding of the relative contribution of each factor in the development of AKI, and provide clinicians with tools to better assess the preoperative risk and help predicting the development of AKI. ACE = angiotensin enzyme converting inhibitor; CO = cardiac output; CPB = cardiopulmonary bypass; HLA = human leukocyte antigens; NADPH = nicotinamide adenine dinucleotide phosphate-oxidase.

arteries can provide information on renal vascular resistance; however, this method does not measure renal blood flow *per se*. Therefore, developing tools to measure renal perfusion (*i.e.*, renal blood flow and distribution of renal microvascular blood flow within the renal parenchyma) will allow a better understanding of the role of renal perfusion in renal damage.

The development of biomarkers of renal injury has been a major step forward. However, further investigation is needed to explore the significance of increased serum and urine levels of biomarkers, including neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, fatty acid-binding protein 1, and α -1 microglobulin, the influence of underlying processes (*e.g.*, systemic inflammation), the influence of comorbidities and their source of production (*i.e.*, extra renal production), and the specificity and sensibility of assays (fig. 4). A combination of methods to assess renal structural injury, renal perfusion, and renal function will likely help develop new strategies and treatments that prevent or limit the development of AKI in surgical and critically ill patients.

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