Renal protection in the 21st century

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Purpose of review
Among critically ill patients, acute kidney injury (AKI) is still a common and serious complication with a tremendous impact on short-term and long-term outcomes. The objective of this review is to discuss strategies for renal protection and prevention of AKI in ICU patients.

Recent findings
It is fundamental to identify patients at risk for AKI as soon as possible and as accurately as possible. In order to achieve these goals, translational approaches implementing new biomarkers have shown promising results. Focusing on the role of potential preventive strategies, hemodynamic stabilization is the most important intervention with proven efficacy. Recent published data undermined any hope that high-dose statin therapy in statin-naïve patients could exert renoprotective effects. However, preliminary data revealed the renoprotective activity of dexmedetomidine when used as a sedative agent. Moreover, several studies demonstrated the protective effects of remote ischemic preconditioning in various organs including the kidneys. The use of balanced crystalloid instead of hyperchloremic solutions also contributes to the reduction of AKI in critically ill patients.

Summary
To prevent AKI, it is crucial to identify patients at risk as early as possible. Establishing hemodynamic stability and an adequate intravascular volume state to ensure a sufficient perfusion pressure is the only effective therapeutic intervention. It is self-evident that nephrotoxic agents should be avoided whenever it is possible.

Keywords
acute kidney injury, critically ill patients, remote ischemic preconditioning, renoprotection

INTRODUCTION

Critically ill patients exhibit a high risk to develop acute kidney injury (AKI) [1]. Despite the intensive efforts undertaken since the beginning of this century, AKI is still associated with higher rates of infections and gastrointestinal bleeding [2,3], worse long-term outcomes [4,5], increased socioeconomic costs [6], and higher mortality [7,8]. This is particularly true for patients with severe AKI requiring renal replacement therapy (RRT) [1,9]. But even patients with only minor changes in serum-creatinine levels are exposed to an increased short-term and long-term mortality [10]. Furthermore, patients with severe dialysis-dependent AKI who survive and are discharged from the hospital show an increased risk for the development of chronic kidney disease (CKD) [4,11▪].

This review discusses current strategies for renoprotection and the prevention of AKI in critically ill patients.

ACUTE KIDNEY INJURY IN THE 21ST CENTURY

In the past, AKI has long been an underdiagnosed and misunderstood disease caused by the absence of a consensus definition and poor knowledge. In 2004, the Acute Dialysis Quality Initiative (ADQI) published the first consensus definition: the RIFLE classification (Risk, Injury, Failure, Loss, and End-stage renal disease) [12]. A number of studies have validated the RIFLE classification. However, since it has been demonstrated that even small increases in serum-creatinine levels are associated with worse outcomes [10], the Acute Kidney Injury Network (AKIN) modified this concept and published the AKIN criteria in 2007 [13]. Most recently the KDIGO guidelines, developed by the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup in 2012 [14], merged both the RIFLE and AKIN criteria. According to the KDIGO guidelines, AKI is

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KEY POINTS

- The first step in the prevention of AKI is early detection of renal injury gathered from the measurement of new urinary biomarkers.
- Ensuring hemodynamic stability to maintain optimal renal perfusion is of paramount importance.
- The conservation of intravascular volume status while avoiding hyperchloremic solutions represents an essential goal.
- No drug has been approved to date for the prevention or therapy of AKI in critically ill patients.
- RIPC might be a simple and safe intervention to protect the kidneys in high-risk patients.

diagnosed when at least one of the following criteria is met: serum-creatinine increase of $\geq$0.3 mg/dl within 48 h, or 1.5 times increase compared with baseline within 7 days, or urinary output less than 0.5 ml/kg/h for $\geq$6 h.

Serum-creatinine and urinary output are the classical biomarkers of kidney function. They both change late in the development of AKI and first emerge when the loss of kidney function has reached an advanced stage. In addition, both markers are influenced by multiple factors such as sex, age, muscle mass, volume status, and medication. Biomarkers which can be employed in the diagnosis of AKI prior to the occurrence of a potentially irreversible loss of kidney function would represent a considerable step forward as compared with the reliance on serum-creatinine levels and urinary output.

Markers of kidney injury

The identification of biomarkers to prevent or to detect early AKI is a key research area. During the last years, several urinary biomarkers have been investigated including neutrophil gelatinase-associated lipocalin (NGAL), the most extensively studied substance, tissue-inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor binding protein-7 (IGFBP-7), which have been introduced most recently [15,16].

In patients with normal kidney function, NGAL is almost undetectable in the urine, but it is significantly upregulated after ischemic and nephrotoxic insults [17–19], leading to the opinion that NGAL is the 'troponin' of the kidneys [20]. However, unlike myocardial infarction, the cause of AKI in the setting of critical illness is multifactorial and not limited to ischemia. Several clinical studies investigated the predictive performance of NGAL for AKI using the area under the receiver operating characteristics curve (AUC_{ROC}) analysis. Results were scattered between a range of 0.54 [21] and 0.99 [22] in critically ill patients. These apparent inconsistencies might be explained by the insensitivity and unspecificity of serum-creatinine levels and urinary output, which were routinely used as 'gold standard' for identifying AKI. The timing of biomarker assessment and the burden of comorbidities may play a further role in explaining the divergent results of urinary NGAL. In fact, this could be demonstrated in a study by McIlroy *et al.* [23]. These authors demonstrated that NGAL only predicted AKI in patients who had normal kidney function prior to the critical illness [23]. Furthermore, it was shown that NGAL levels are elevated in patients with CKD [24]. The NGAL molecule is produced by a number of tissues but in different molecular compositions [25]. Current tests are not suitable to differentiate between the numerous isoforms and fail to identify the renal NGAL. Therefore, the use of NGAL as a reliable biomarker of AKI in critically ill patients must be viewed in a critical light [26].

TIMP-2 and IGFBP-7 are both involved in the G1 cell cycle arrest, which affects tubular cells with damaged DNA to prevent their division. These biomarkers are both upregulated in renal tubular stress situations and demonstrated the best performance in the Discovery trial wherein 32 different biomarkers for the prediction of severe AKI (KDIGO stages 2 and 3) were tested [15]. Furthermore, they have been validated in the Sapphire trial in 728 critically ill patients. The AUC_{ROC} of 0.80 for the combination of TIMP-2 $\times$ IGFBP-7 was superior in comparison to all other biomarkers tested ($P < 0.002$) [15]. In addition, it has been demonstrated recently in a small cohort of critically ill patients that IGFBP-7 levels predict mortality, renal recovery, and severity of AKI [27]. As shown previously, TIMP-2 $\times$ IGFBP-7 levels above 0.3 had a sensitivity of 92% for the development of moderate or severe AKI during the next 12 h [28]. According to the 'renal angina concept' wherein it was postulated to measure biomarkers in patients with clinical risk factors for the development of AKI [29], a recommendation for the clinical application of TIMP-2 $\times$ IGFBP-7 in the critical care setting has recently been published [30▪▪]. Thus, these new biomarkers may be the first step in the prevention of AKI in the 21st century.

RENOPROTECTIVE INTERVENTIONS

Great efforts to develop effective interventions for the prevention and treatment of AKI in order to

improve long-term outcomes of critically ill patients have been made, even though with little success.

Hemodynamic stabilization

Physiologically, renal blood flow (RBF) is autoregulated within a wide range of arterial blood pressure (BP) levels to ensure that the glomerular filtration rate (GFR) can be kept constant. However, autoregulation might be impaired because of underlying diseases (e.g., cardiogenic or hemorrhagic shock) or preexisting conditions (e.g., arterial hypertension). In compromised patients, hypotension may lead to a decrease in renal perfusion and consequently to AKI. This was demonstrated in a retrospective study of 274 septic patients wherein BP drops below a threshold of 75 mmHg mean arterial blood pressure (MAP) were associated with the need for RRT [31,32]. A small study of cardiac surgery patients showed improved renal oxygen saturation and GFR when MAP was restored from 60 mmHg to 75 mmHg [33]. Moreover, in a substudy of a prospective observational trial of 423 critically ill patients with severe sepsis, the authors examined the association of hemodynamic data with the progression of AKI defined as new onset of AKI or worsening of AKI by at least one KDIGO stage during the first 5 days of ICU admission [34]. Of these 423 patients, 153 (36.2%) met the primary endpoint (24.1% had a new onset of AKI and 12.1% had a worsening of at least one KDIGO stage). These patients showed significantly lower time-adjusted MAP of 74.4 mmHg (63.8–80.8 mmHg) compared with those without progression, 78.6 mmHg (72.9–85.4 mmHg; $P < 0.001$). It is not known which vasopressor is the most effective for the prevention of AKI but for restoration of MAP in acute circulatory failure, the guidelines recommend the use of norepinephrine as first choice vasopressor. Di Giantomasso *et al.* [35] demonstrated in an experimental hypotensive model that norepinephrine significantly increased global and medullary RBF and restored vascular tone. Vasopressin is an alternative drug to augment BP and to increase diuresis. Russell *et al.* [36] performed a multicenter randomized-controlled trial (RCT) in 778 patients with septic shock. Patients were assigned to receive either norepinephrine alone or in combination with vasopressin. The authors found no significant differences in the vasopressin group as compared with the norepinephrine group in 28-day (35.4 vs. 39.3%; $P = 0.26$) and 90-day mortality (43.9 and 49.6%; $P = 0.11$). However, in a post-hoc analysis of this trial the authors found a trend toward a lower rate of progression of RIFLE 'Risk' to RIFLE 'Failure' or 'Loss' in the vasopressin group (20.8 vs. 39.6%; $P = 0.03$) and a lower rate of RRT (17.0 vs. 37.7%; $P = 0.02$) [37].

A definition of what is the optimal perfusion pressure in an individual patient cannot be specified. Asfar *et al.* [38] showed no significant difference in the incidence of AKI in patients with a higher target MAP of 80–85 mmHg compared with a lower target of 65–70 mmHg, whereas Badin *et al.* [39] found a MAP of 72–82 mmHg to be necessary to prevent AKI in patients with septic shock. Among patients with chronic hypertension, the need for RRT was significantly reduced in higher target BP [38]. This elucidates that optimal blood pressures for each individual considering the underlying disease and the premorbid conditions are crucial to ensure adequate renal perfusion pressure and prevent AKI. This is in line with recommendations of the Surviving Sepsis Campaign targeting a MAP of at least 65 mmHg individualizing this value according to the pre-existing conditions [40]. To achieve this goal, the KDIGO guidelines recommend to combine the continuous infusion of vasopressors with appropriate volume loading [32]. The clinical context determines the choice of vasopressor agent in the individual patient.

Statins

3-Methoxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are mainly used to reduce cholesterol levels in the prevention of cardiovascular diseases. Pleiotropic effects through nonlipid related mechanisms (e.g., improvement of endothelial dysfunction, increased nitric oxide bioavailability, inhibition of inflammatory responses, stabilization of atherosclerotic plaques, and antioxidant properties) have led to the suggestion that statins may also reduce the incidence of AKI.

Quintavalle *et al.* [41] performed a RCT of high-dose atorvastatin (80 mg) before contrast media exposure in 410 patients with CKD. The incidence of AKI was significantly lower in the atorvastatin group (4.5%) compared with the control group (17.8%) [$P = 0.005$; odds ratio (OR) 0.22; 95% confidence interval (CI) 0.07–0.69]. However, more recently published data do not support these results. Billings *et al.* [42▪▪] conducted a double-blinded placebo-controlled, randomized clinical trial of 199 statin-naïve adult patients undergoing cardiac surgery. Patients were allocated to receive either high-dose statin treatment (80 mg of atorvastatin the day before surgery, 40 mg the morning of surgery, and 40 mg the day after surgery) or placebo. AKI occurred in 21.6% in the atorvastatin group vs. 13.4% in the placebo group ($P = 0.15$). The same authors analyzed 416 patients pretreated with

statins and randomized them to statin (receiving additionally 80 mg of atorvastatin the morning of surgery and 40 mg the morning after) or placebo. In the patients already taking statins, the incidence of AKI was 20.4 vs. 22.4% in the placebo group ($P = 0.63$).

Preventive treatment with statins has mainly been studied in the perioperative setting or in patients with contrast media exposure. But, Murugan *et al.* [43] analyzed the effect of statin use in a multicenter, prospective cohort study of 1836 patients with community-acquired pneumonia and found no effect of statins on the incidence of AKI. Among patients with AKI, statins did not reduce the all-cause 1-year mortality. In conclusion, based on the available evidence preventive treatment with statins cannot be recommended.

Dexmedetomidine

The highly selective alpha-2 agonist dexmedetomidine (Dex) is used in the intensive care setting because it has many desirable effects including analgesia, anxiolysis, inhibition of central sympathetic outflow, and reduction of norepinephrine release thus improving hemodynamic stability and balancing the myocardial oxygen supply/demand ratio.

In animal studies, Dex has been shown to provide cytoprotection following renal ischemia [44] and to ameliorate hypoxemia-induced apoptosis in proximal tubular cells [45▪]. In a cohort of 1133 patients undergoing cardiac surgery, 567 patients received Dex postoperatively [46]. The incidence of AKI was significantly reduced in the Dex group (26.1%) as compared with the control group (33.75%; $P = 0.0089$). This was especially true for patients with preoperative normal or mild impairment of kidney function. Balkanay *et al.* [47] performed a prospective-randomized, triple-blinded study of different doses of Dex (placebo; low dose: <8 μg/kg, high dose: ≥ 8 μg/kg) in 90 patients undergoing elective cardiac surgery and analyzed the effect on the biomarker NGAL, a biomarker for kidney cellular damage. They found a dose-dependent effect of Dex with the lowest increase in NGAL with the higher Dex dose. But, regarding the conventional tests for detecting AKI (serum-creatinine and urinary output), they found no differences in the three groups.

Dex seems to be a promising pharmacological approach in terms of prevention of AKI. So far, most of the studies dealing with Dex and AKI have been performed in animals or in cardiac surgery patients. Large RCTs in critically ill patients are needed to clearly determine the effects of Dex on AKI.

Remote ischemic preconditioning

Remote ischemic preconditioning (RIPC) is an intervention consisting of transient episodes of sublethal ischemia and reperfusion injury to a remote tissue or organ before the subsequent injury occurs. The underlying mechanisms are not fully understood but recent evidence suggests that RIPC may prevent the development of AKI.

Several studies have been performed but the results are controversial. Zimmerman *et al.* [48] performed a randomized-controlled study of RIPC in 120 patients undergoing cardiac surgery with cardiolpulmonary bypass (CPB). Twelve patients in the RIPC (20%) vs. 28 patients in the Sham-RIPC group (47%) developed an AKI in the postoperative period [absolute risk reduction (ARR): 27%; $P = 0.004$]. Zarbock *et al.* [49▪▪] performed a randomized-controlled multicenter trial on 240 high-risk patients undergoing cardiac surgery. They compared RIPC vs. Sham-RIPC and found a 15% reduction of AKI when RIPC was applied (37.5% RIPC vs. 52.5% Sham-RIPC; $P = 0.02$). On the other hand, Choi *et al.* [50] analyzed the effect of RIPC in 76 patients undergoing complex valve surgery. Primary outcomes were the incidence of AKI and changes in renal biomarkers. They found no differences in the occurrence of AKI or in the concentrations of biomarkers in both groups. Gallagher *et al.* [51] published a RCT of RIPC in 86 patients with CKD undergoing coronary artery bypass graft (CABG). They defined the primary outcome of AKI as an increase in serum-creatinine of 0.3 mg/dl within 48 h after surgery. The results showed no difference between both groups. The authors concluded that RIPC had no effect on the incidence of AKI after CABG in CKD patients. Two other RCTs on the effect of RIPC in cardiac surgery patients have recently been published [52,53]. The authors used combined primary outcomes but showed no effect of RIPC on AKI in secondary analyses.

RIPC has also been studied in nonsurgery patients. Igarashi *et al.* [54] analyzed the effect of RIPC on the incidence of liver fatty acid binding protein (L-FABP) based contrast-induced acute kidney injury (CI-AKI) in 60 patients with moderate CKD and showed a 19.2% ARR when treated with RIPC ($P = 0.038$). Yamanaka *et al.* [55] demonstrated in 96 patients undergoing emergency percutaneous coronary intervention an ARR of 26% (OR 0.18; 95% CI 0.05–0.64; $P = 0.008$).

Until now, RIPC has only been analyzed in the non-ICU setting. A large multicenter trial of RIPC in critically ill patients is required to prove the therapeutic value.

Intravenous fluids

The application of intravenous fluids to maintain hydration or increase intravascular volume is a frequent intervention in critically ill patients. 0.9% sodium (saline) is the most commonly used crystalloid solution. However, despite the frequent use, the 'physiological saline 0.9%' contains unphysiologically high amounts of chloride providing uncertainty about the safety in critically ill patients. Saline infusion may cause hyperchloremic acidosis leading to renal vasoconstriction and consequently to a reduction of GFR [56]. In fact, a retrospective analysis of 23 000 patients undergoing noncardiac surgery found in 22% of all patients an acute postoperative hyperchloremia associated with an increased incidence of renal dysfunction defined as stage RIFLE-R (12.9 vs. 9.2%; $P < 0.01$) [57]. In a substudy of the prospective FINNAKI study, the authors found severe hyperchloremia (chloride >114 mmol/l) in one of 10 ICU patients and an independent risk factor of higher time-weighted chloride for AKI [58]. Buffered and balanced crystalloid solutions might be an alternative with electrolyte concentrations, which more closely resemble that of plasma. In a retrospective analysis including 53 448 critically ill patients with sepsis comparing balanced and nonbalanced fluid therapy, lower AKI rates were found in the balanced fluid group [59]. Following a propensity-matched analysis, balanced fluid therapy was associated with lower in-hospital mortality as compared with nonbalanced fluid therapy [19.6 vs. 22.8%; response rate (RR) 0.86; 95% CI 0.78–0.94; $P = 0.001$], but there was no significant difference in the incidence of AKI with (4.5 vs. 4.7%; RR 0.95; 95% CI 0.76–1.19) and without dialysis (7.1 vs. 7.5%; RR 0.95; 95% CI 0.78–1.15). In line with these results, a recently published RCT in 2278 critically ill patients showed no significant reduction of AKI if buffered crystalloids were applied [60▪▪]. In detail, in four ICUs in New Zealand 2278 critically ill patients were randomized to receive either saline or a buffered crystalloid solution. The primary outcome was the proportion of patients with AKI defined as a rise in serum-creatinine levels of at least two-fold or a serum-creatinine ≥3.96 mg/dl with an increase of ≥0.5 mg/dl. The results showed no significant difference in the incidence of AKI (9.6 in the buffered crystalloid vs. 9.2% in the saline group; RR 1.04; 95% CI 0.80–1.36; $P = 0.77$), RRT treatment (3.3 vs. 3.4%; RR 0.96; 95% CI 0.62–1.50; $P = 0.91$), and in-hospital mortality (7.6 vs. 8.6%; RR 0.88; 95% CI 0.67–1.17; $P = 0.40$). Furthermore, the incidence of acidemia with a pH less than 7.20 was not equal in both groups (1.1 vs. 0.8%; $P = 0.52$).

In summary, currently it is unclear whether balanced solutions are superior to physiological saline. However, some evidence suggests that balanced solutions might be safer.

CONCLUSION

AKI is a common complication in critically ill patients. With the knowledge that even small increases in serum-creatinine levels are associated with increased mortality, the goal of early detection of AKI has gained importance. The implementation of new biomarkers and risk stratification indices has produced positive results with respect to the identification of patients at risk for AKI. In the past few years, efforts have been made to identify strategies for the prevention of AKI. However, renoprotective treatment remains limited to the maintenance of hemodynamic stability and the optimization of the intravascular volume state while avoiding nephrotoxic agents. Unfortunately, up to now no pharmacological agent with proven benefits has been detected. Evidence suggests that RIPC might be a safe and useful intervention but this needs to be demonstrated in the critical care setting. Ensuring an adequate renal perfusion pressure is the most important and effective treatment.

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Conflicts of interest

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This RCT show that saline application compared with buffered crytsalloids in critically ill patients is not associated with an increased incidence of AKI.