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Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017

Expert opinion of the Working Group on Prevention, AKI section, European Society of Intensive Care Medicine

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Abstract

Background: Acute kidney injury (AKI) in the intensive care unit is associated with significant mortality and morbidity.

Objectives: To determine and update previous recommendations for the prevention of AKI, specifically the role of fluids, diuretics, inotropes, vasopressors/vasodilators, hormonal and nutritional interventions, sedatives, statins, remote ischaemic preconditioning and care bundles.

Method: A systematic search of the literature was performed for studies published between 1966 and March 2017 using these potential protective strategies in adult patients at risk of AKI. The following clinical conditions were considered: major surgery, critical illness, sepsis, shock, exposure to potentially nephrotoxic drugs and radiocontrast. Clinical endpoints included incidence or grade of AKI, the need for renal replacement therapy and mortality. Studies were graded according to the international GRADE system.

Results: We formulated 12 recommendations, 13 suggestions and seven best practice statements. The few strong recommendations with high-level evidence are mostly against the intervention in question (starches, low-dose dopamine, statins in cardiac surgery). Strong recommendations with lower-level evidence include controlled fluid resuscitation with crystalloids, avoiding fluid overload, titration of norepinephrine to a target MAP of 65–70 mmHg (unless chronic hypertension) and not using diuretics or levosimendan for kidney protection solely.

Conclusion: The results of recent randomised controlled trials have allowed the formulation of new recommendations and/or increase the strength of previous recommendations. On the other hand, in many domains the available evidence remains insufficient, resulting from the limited quality of the clinical trials and the poor reporting of kidney outcomes.

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Professor Groeneveld succumbed to a long illness which he fought with typical determination during the updating of this paper. He is sadly missed by us all.

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Keywords: Acute kidney injury, Systematic review, Recommendations, Prevention, Volume expansion, Vasopressors

Introduction

Acute kidney injury (AKI) affects up to 50% of critically ill patients and is independently associated with both short- and long-term morbidity and mortality [1–5]. The recent AKI-EPI study demonstrates that the most frequent causes of AKI in the critically ill are sepsis and hypovolaemia followed by nephrotoxic agents [6]. However, the cause of AKI is often multifactorial with pre-existing co-morbidities further increasing the risk [3, 7–9].

The aim of this systematic review on the prevention and avoidance of further progression of AKI, by core members of the AKI section of the ESICM, is to provide:

- A critical evaluation of the existing evidence
- Give recommendations for clinical practice
- Update our previously published recommendations [10] and most recent guidelines [2, 11]

Our recommendations principally concern critically ill patients on the ICU but can also be applied to those planned to be admitted to the ICU such as high-risk surgical patients. By consensus, we primarily focussed on the role of volume expansion, diuretics, inotropes, vasopressors/vasodilators, hormones, nutrition, statins, sedatives and ischaemic preconditioning.

Methodology

A systematic search of the literature was performed using the following databases: MEDLINE (1966 through March 2017), EMBASE (1980 through March 2017), CINAHL (1982 through March 2017), Web of Science (1955 through March 2017) and PubMed/PubMed CENTRAL to identify key studies, preferably randomised (placebo) controlled trials (RCT) and meta-analyses, addressing strategies to prevent AKI in *adult* critically ill patients. The following *clinical conditions* were considered: major surgery, critical illness, sepsis, shock and exposure to potentially nephrotoxic drugs. Specifically, renal transplantation, primary intrinsic renal disease (e.g. vasculitis) and hepatorenal syndrome were *not* considered. Search strategy and endpoints are available as electronic supplementary material (ESM_1).

These recommendations are intended to provide clinical guidance and involved a modified Delphi process with a consensus meeting during the annual congresses of the European Society of Intensive Care Medicine in 2014, 2015 and 2016 followed by electronic-based/telephone discussions. The quality of the evidence was judged by using the most recent GRADE (Gradings of Recommendations, Assessment, Development and Evaluation) criteria (Fig. 1) [12, 13]. The strength of the recommendations was classified as either strong (Grade 1) or weak (Grade 2). The degree (i.e. quality) of evidence for the recommendations was classified from high (A) to very low (D) according to factors including study design consistency of the results and directness of the evidence (Fig. 1, ESM_1 Table S1). Evidence was downgraded where there was a risk of bias, inconsistency and imprecision. Evidence was upgraded for large effect size or significant dose–response gradient. If benefit or harm was unequivocal, but evidence was difficult to categorize by the GRADE methodology, we used best practice statements (BPSs), which represent ungraded strong recommendations [14] (Table 1).

We acknowledge that there may be circumstances whereby a recommendation cannot or should not be followed for an individual patient. Furthermore, interventions are generally investigated in isolation and not in combination, and as such recommendations relate to the *primary* intervention. Local clinical guidelines will govern the use of either a single intervention or a combination thereof.

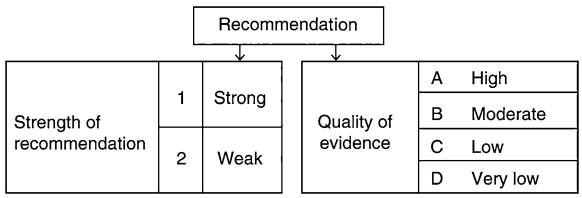

Fig. 1 Grade system for grading recommendations (Modified from Guyatt et al. [12])

Table 1 Criteria for best practice statements (Modified from Guyatt et al. [14])

	Criteria for best practice statements
1	Is the statement clear and actionable?
2	Is the message necessary?
3	Is the net benefit (or harm) unequivocal?
4	Is the evidence difficult to collect and summarize?
5	Is the rationale explicit?
6	Is this better to be formally GRADEd?

GRADE Gradings of Recommendations, Assessment, Development, and Evaluation

Volume expansion

Recommendations

1. We *recommend* controlled fluid resuscitation in volume depletion, while, however, avoiding volume overload (Grade 1C).
2. We *recommend* against the use of starches (Grade 1A) as harm has been shown and *suggest* not using gelatine or dextrans for fluid resuscitation (Grade 2C).
3. We *recommend* correction of hypovolaemia/dehydration using isotonic crystalloids in patients receiving intravascular contrast media (Grade 1B).
4. We *recommend* regular monitoring of chloride levels and acid–base status in situations where chloride-rich solutions are used (BPS).
5. We *suggest* the use of balanced crystalloids for large volume resuscitation (Grade 2C).
6. We *suggest* using human serum albumin if a colloid is deemed necessary for the treatment of patients with septic shock (Grade 2C).
7. We *suggest* prophylactic volume expansion with crystalloids to prevent AKI by certain drugs (specified below) (BPS).
8. We *suggest* not delaying urgent contrast-enhanced investigations or interventions for potential preventative measures (BPS).

Rationale

Relative and overt hypovolaemia are significant risk factors for development of AKI [15–18]. Timely fluid administration can restore circulating volume and renal perfusion, and may also reduce nephrotoxicity [19]. Volume replacement should be performed in a controlled, monitored fashion [20] as injudicious use of fluids carries its own inherent risks and may even contribute to AKI by increasing renal interstitial oedema and renal parenchymal pressure [21, 22]. Moreover, goal-directed therapy including the use of central venous pressure (CVP) as a resuscitation target has not been shown to prevent AKI in sepsis [23]. Volume replacement may be through crystalloids, colloids or their combination. Isotonic crystalloids represent the mainstay for correcting extracellular volume depletion with the caveat that hyperchloraemia is prevented to reduce potential renal vasoconstriction [24, 25]. Compared to crystalloids, colloids theoretically result in a greater plasma expansion. However, this effect depends on vascular barrier integrity which may be compromised in sepsis, particularly in the presence of vasoplegia [26, 27]. Consequently, the difference in required volumes for fluid resuscitation was minimal between crystalloids and colloids in large RCTs [28]. Moreover, large volume replacement with colloids alone risks hyperoncotic impairment of glomerular filtration [29, 30] and osmotic tubular damage [31, 32].

Available artificial colloids include gelatines, dextrans and until recently, starches. Gelatines have a moderate volume effect. Although risk of osmotic nephrosis with gelatines exists [33], the lack of clear clinical data on deleterious effects on renal function [34, 35] is offset by the possible prion transmission, histamine release and coagulopathy [36, 37]. Dextrans have reasonably high volume effects although anaphylaxis, coagulation disorders, osmotic nephrosis and AKI may occur with doses above 1.5 g/kg/day [38–41]. Human albumin (HA) is the only naturally occurring colloid and may appear attractive in hypooncotic hypovolaemia. It does increase the response to diuretics in patients with hypoalbuminaemia (e.g. nephrotic syndrome) [42, 43], has no negative effects on kidney function [44, 45], is safe [46] but can be costly.

Clinical studies

Unsurprisingly, no studies have specifically addressed the effects of volume expansion compared to no volume resuscitation in overt hypovolaemia given the intuitive benefits of volume replacement. In severe sepsis, the beneficial effects of timely volume replacement on organ failure and mortality are well known, although the first RCT proving benefit of early volume resuscitation did not report kidney function [47]. On the other hand, preoperative volume expansion failed to reduce the incidence of postoperative AKI ins 328 patients undergoing cardiac surgery [48], and a recent pilot RCT in sepsis could demonstrate that a volume-restrictive fluid protocol can reduced the incidence of AKI (RR 0.32; 95% CI 0.32–0.96) [49].

Crystalloids are considered the mainstay for volume expansion. Observational studies suggest an increased risk of AKI, renal replacement therapy (RRT) and mortality associated with the use of large volumes of normal saline (0.9% NaCl) as compared to so-called balanced solutions where chloride is partially replaced by another metabolizable anion [50–52]. An RCT comparing saline to a balanced solution (Plasmalyte®) in 2278 patients treated in four ICUs failed to show any superiority of balanced crystalloids regarding renal outcomes [53]. The study has been criticized for the limited fluid doses, inclusion of patients with low disease severity and the absence of data on chloride levels [54]. Similar results were observed in the pilot cluster-randomised, multiple-crossover SALT trial comparing saline to a balanced solution in 974 critically ill adults [55]. Again, only modest volumes were used, but increased rates of AKI were found in the normal saline group if larger volumes were administered (ESM_2 Table S2). Studies on the effectiveness of sodium bicarbonate in preventing AKI, predominantly in patients undergoing cardiac surgery, have produced

conflicting results [56–59] as have consecutive meta-analyses [60–63].

The effect of *colloids* on renal function has undergone extensive scrutiny over the last decade. Large RCTs have substantiated the increased risk of AKI and RRT with use of starches [64] particularly in sepsis [65, 66], where they also lead to increased mortality [66] (ESM_2 Table S3). This is verified by several meta-analyses [67–70] which underpin the abandoning of starches in critically ill patients [20, 71, 72]. Clinical data on the effects of gelatine on renal function are scarce. A recent meta-analysis, including three trials in 212 patients comparing gelatins with crystalloids or albumin, indicated a 35% increased relative risk of developing AKI with gelatine [73].

In contrast to artificial colloids, the administration of albumin appears to be safe for the kidney. A large RCT comparing normal saline to 4% HA in various clinical settings failed to demonstrate any differences in renal function [46] (ESM_2 Table S3). In the ALBIOS trial the use of hyperoncotic (20%) albumin showed no effect on AKI or need for RRT in severe sepsis [74] but enabled a less positive fluid balance, confirming the results of another small trial [75]. A post hoc analysis of the ALBIOS trial showed survival benefit in septic shock [74] confirmed by meta-analyses [76, 77]. Hypoalbuminaemia in cardiac surgery might be another indication with improved fluid balance as well as a reduced rate of AKI being observed in a single-centre RCT of 220 patients [78].

Hypovolaemia may also contribute significantly towards drug-induced renal injury, although the available evidence supporting preventative hydration is only observational with no consensus related to timing, optimal volume and type of solution [19, 79, 80]. Prophylactic volume expansion has been shown to prevent harm from amphotericin B, antivirals including foscarnet, cidofovir and adefovir [81–83] as well as drugs causing crystal nephropathy such as indinavir, acyclovir, and sulfadiazine [84].

Prophylactic volume expansion is the mainstay of all recommendations to prevent contrast-associated AKI (CA-AKI) and is based on several randomised controlled studies performed in non-critically ill patients [85–90]. However, studies comparing hydration to no hydration are scarce [91]. Several pitfalls should be considered. First, CA-AKI is a diagnosis of exclusion and considerable variation exists with regard to the reported incidence rates, which are confounded by many factors such as transient fluctuations in measured serum creatinine in hospitalised patients and use of non-standardised diagnostic criteria [92]. Secondly, CA-AKI does not occur in patients without other risk factors for AKI, whereas most critically ill patients receiving intravascular contrast have other risk factors. Moreover, individuals with high risk for CA-AKI may not be given contrast. For these reasons the role of CA-AKI is uncertain, particularly in an era where the use of low- or iso-osmotic agents and lower contrast volume administration have become standard practice. As indicated by an analysis of the Nationwide Inpatient Sample dataset comprising 5, 931,523 hospitalisations the OR for CA-AKI adjusted for age, sex, mechanical ventilation and combined co-morbidity score was 0.93 (0.88–0.97) [93]. Whereas a retrospective single-centre cohort study in 747 critically ill patients showed a rate of CA-AKI of 16% [94], matched cohort studies could not demonstrate a relationship with IV contrast for computed tomography in the ICU [95–97] or emergency department [98]. These findings are supported by a systematic review and Bayesian meta-analysis [99]. In the most recent propensity-matched cohort study, IV contrast was not associated with an increased risk of AKI or dialysis, but a subgroup with pre-CT eGFR of at most 45 ml/min/1.73 m^2 showed an increased risk of dialysis. The numbers in this subgroup were, however, small and subject to selection bias [97].

Although it seems prudent to correct hypovolaemia before contrast administration, prophylactic volume expansion in critically ll patients who are euvolaemic cannot be recommended on the basis of current data. No study demonstrates protection of pre-emptive volume expansion against CA-AKI in the critically ill. An RCT comparing hydration with isotonic bicarbonate versus normal saline failed to show superiority of either regimen but reported an excessively high rate of CA-AKI of 33% in both groups [100], which may be attributed to severity of illness in this critically ill cohort. Importantly, in patients with chronic kidney disease (CKD) undergoing percutaneous coronary intervention (PCI), hydration volumes above 11 ml/kg body weight (BW) were associated with continuously increased rates of AKI, requirement for RRT and mortality. The adjusted OR for developing AKI with hydration volumes greater than 25 ml/kg BW was 2.11 (CI 1.24–3.59) [101]. We recommend that the clinical decision to perform a contrast study in ICU patients must weigh the potential benefits with the low but probably not zero risk of CA-AKI.

Diuretics

Recommendations

1. We *recommend* against loop diuretics given solely for the prevention of acute kidney injury (Grade 1B).
2. We *suggest* using diuretics to control or avoid fluid overload in patients that are diuretic-responsive (Grade 2D).

Rationale

Oligoanuria is frequently the first indicator of acute renal dysfunction. Intensivists frequently use loop diuretics in

a wide spectrum of AKI settings [102]. The rationale for using diuretics to ameliorate AKI includes prevention of tubular obstruction, reduction in medullary oxygen consumption and increase in renal blood flow as well as reducing fluid overload and venous congestion [103–105]. Although there is no single parameter for fluid overload, increased CVP [106], peripheral oedema [107] and/or increased intra-abdominal pressure [108, 109] may be used as surrogates. A recent study demonstrated than a urinary output of at least 100 ml/h following a test dose of 1.0–1.5 mg furosemide/kg BW predicted reduced progression to a higher stage of AKI in oliguric patients [110].

Clinical studies

Use of conservative fluid management including diuretics has been investigated in only one large RCT in patients with acute lung injury (FACTT trial) which showed a tendency to reduced requirement of RRT [111].

In cardiac surgery either no protection [112] or elevated postoperative serum creatinine levels were found in patients receiving furosemide [113]. These findings were supported by a recent meta-analysis [114]. In patients with acute heart failure, diuretic therapy with higher doses was more effective at reducing clinical symptoms, but at the cost of decreased renal function [115]. To date four RCTs have examined the role of diuretics in *established* renal failure in the intensive care setting. No demonstrable improvements in clinically relevant outcomes, such as recovery of renal function or mortality, were observed [31, 116–118]. Other studies compared diuretics with dopamine or placebo, again with no perceived benefit [119–121]. Three meta-analyses confirmed that the use of diuretics in established AKI did not alter outcome but carried a significant risk of side effects such as hearing loss [122–124] (ESM_2 Table S4).

Vasopressors

Recommendations

1. We *recommend* titrating vasopressors to a mean arterial pressure (MAP) of 65–70 mmHg (Grade 1B) rather than a higher MAP target (80–85 mmHg) in patients with septic shock. However, for patients with chronic hypertension we *recommend* aiming for a higher target (80–85 mmHg) for renal protection in septic shock (Grade 1C).
2. We *recommend* lowering systolic pressure to 140–190 mmHg rather than to 110–139 mmHg in patients with acute cerebral haemorrhage with severe admission hypertension (Grade 1C).
3. If vasopressors are needed for treatment of hypotension, we *recommend* norepinephrine (along with correction of hypovolaemia) as the first-choice vasopressor to protect kidney function (Grade 1B) and *suggest* vasopressin in patients with vasoplegic shock after cardiac surgery (Grade 2C).
4. We *suggest* individualizing target pressure when premorbid blood pressure is available (BPS).

Rationale for MAP target

Preservation or improvement of renal perfusion can theoretically be achieved through increasing cardiac output by fluid resuscitation or inotropic drugs, through renal vasodilators or systemic vasopressors. Optimal target mean arterial pressure (MAP) was studied in a large open-label multicentre RCT randomising 777 patients with septic shock to resuscitation with a MAP target of either 80–85 mmHg or 65–70 mmHg [125]. In most of the patients the achieved MAP was above the set target. The study found no difference in mortality, incidence of AKI stage 2 (38.7% vs. 41.5%, $p = 0.42$) or need for RRT (33.5% vs. 35.8%, $p = 0.5$), but more atrial fibrillation in the high target group. However, in patients with known chronic hypertension a higher MAP resulted in a lower incidence of AKI stage 2 (38.9% vs. 52%, $p = 0.02$) and less RRT (31.7% vs 42.2%, $p = 0.046$); mortality was unchanged.

The safety of lowering systolic pressure was studied in a larger RCT in patients with acute cerebral haemorrhage with severe hypertension on admission [126]. Patients were randomised to a systolic blood pressure target of 110–139 or 140–179 mmHg. The primary endpoint (death or disability) was not different between groups. However, the rate of serious renal adverse events was higher in the lower target group (9% vs. 4%, $p = 0.002$) (ESM_2 Table S5).

Rationale for choice of vasopressor

Norepinephrine is the most commonly used vasopressor in patients with vasodilatory shock. A large RCT comparing dopamine to norepinephrine as initial vasopressor in patients with shock found no difference in mortality between randomised groups. However, norepinephrine was associated with less tachycardia in the first hours and was superior regarding survival in cardiogenic shock patients. In addition, there was a trend towards more RRT-free days through day 28 in the norepinephrine group [127].

Vasopressin or the analogue terlipressin may have a role in the treatment of norepinephrine-refractory shock [128]. Exogenous vasopressin has vasoconstrictive and antidiuretic properties and may increase glomerular filtration by preferential post-glomerular vasoconstriction [129]. In the largest RCT in septic shock (VASST trial), vasopressin reduced mortality in the subgroup with less severe shock, but not in the entire population. There were

no differences in RRT-free days [130]. However, in a secondary analysis, a reduced progression to higher stages of AKI could be demonstrated in the subgroup of patients with AKI stage 1 at baseline [131]. In a subsequent 2 × 2 RCT in 409 patients with early septic shock (VANISH trial) [132], the use of vasopressin compared to norepinephrine did not affect the proportion of patients who never developed AKI stage 3 (57% vs. 59.2%), the number of AKI stage 3-free days [difference −4 (−11 to 5)] or the incidence of AKI stage 3 [difference −5.1% (−15.2 to 5.0)]. The use of vasopressin reduced the need for RRT (difference −9.9% (−19.3 to −0.6), but only in non-survivors. A recent single-centre RCT in 300 patients with vasoplegic shock after cardiac surgery compared noradrenalin to vasopressin as first-choice vasopressor. The use of vasopressin was associated with less acute renal failure (10.3% vs. 35.8%, $p < 0.0001$) and less RRT (2.7% vs. 13.9%, $p = 0.0016$) [133]. This trial, however, had some design issues (e.g. change in primary outcome during the study) and requires confirmation. The studies are summarized in ESM_2 Table S5.

Use of vasodilators

Recommendations

1. We *recommend* against low-dose dopamine for protection against AKI (Grade 1A).
2. We *recommend* not using levosimendan for renal protection in patients with sepsis (Grade 1B) and *recommend* against its use for renal protection in cardiac surgery patients with poor preoperative left ventricular function or needing postoperative haemodynamic support (Grade 1B).
3. We *suggest* not using fenoldopam or natriuretic peptides for renal protection in critically ill or cardiovascular surgery patients at risk of AKI (Grade 2B).

Rationale

Early in the course of ischaemic AKI, renal blood flow (RBF) falls because of stimulation of the sympathetic nervous system and the release of vasoconstrictors such as endothelin, angiotensin II and vasoconstrictive prostaglandins [134, 135]. In contrast, during septic AKI global RBF seems to be well preserved [136, 137]. The main perfusion problem during sepsis seems to occur at the microvascular level and regionally in the outer medulla [138]. When using vasodilators for kidney protection, several issues should be considered. First, vasodilators may cause hypotension by counteracting compensatory vasoconstriction, thus unmasking occult hypovolaemia. Hypotension may further compromise renal perfusion and correction of hypovolaemia is therefore crucial. Second, as a result of endothelial damage, nitric oxide (NO)-dependent vasodilators seem to be ineffective [135]. Third, timing may be crucial, since delayed administration reduces effectiveness as a result of occlusion of the microcirculation [139].

Clinical studies

Low-dose or *'renal' dose dopamine* has been advocated in the past to prevent selective renal vasoconstriction in a variety of conditions. This may not be the case in complex clinical conditions, where low-dose dopamine may even worsen renal perfusion [140]. Several meta-analyses have concluded that 'renal-dose' dopamine has no benefit in either preventing or ameliorating AKI in the critically ill [141–143], the latest [141] being presented in ESM_2 Table S6.

Fenoldopam is a pure dopamine-A_1 receptor agonist providing systemic and renal vasodilation and natriuresis, and it has been studied in cardiovascular surgery and critically ill patients. Two older meta-analyses, one including 1290 critically ill and surgical patients (mainly cardiovascular) from 16 RCTs and the other including 1059 cardiac surgery patients from 13 (partially overlapping) RCTs and case-matched studies, reported that the use of fenoldopam reduced the incidence of AKI, need for RRT and hospital mortality [144]. Most studies were small with a moderate to high risk of bias and in the second meta-analysis 30% of the included studies were abstracts. The two most recent meta-analyses in cardiac surgery and major surgery used stricter inclusion criteria [145, 146] and only found a lower risk for AKI, but not for RRT or death. In addition, both showed an increased risk of hypotension and most included studies had a high risk of bias due to low sample size and fragility index, and use of different definitions for AKI. The most recent and largest RCT in *post cardiac surgery* patients with AKIN stage I [147] did not show any renal protection or clinical benefit from the use of fenoldopam, while fenoldopam conferred more hypotension. (Studies are summarized in ESM_2 Table S7).

Atrial natriuretic peptide (ANP) is produced by cardiac atria in response to an acute increase in stretch and/or pressure and induces afferent dilatation and efferent vasoconstriction, thereby increasing glomerular filtration and urinary sodium excretion with a dose-dependent hypotensive effect [148, 149]. *B-type (brain) natriuretic peptide (BNP)* is primarily produced in the cardiac ventricles and has similar effects [150, 151].

The two most recent meta-analyses including RCTs in the cardiac and cardiovascular surgery population found that the prophylactic infusion of low-dose ANP reduced postoperative peak creatinine [152] and the need for RRT [152–154]. However, the latter was based on only 24 cases of RRT in 563 patients. No effect was found in established AKI and high-dose ANP was associated with more

frequent adverse effects (arrhythmias, hypotension) [154]. Two later RCTs on the use of ANP in aortic arch ($n = 42$) and high-risk cardiac surgery ($n = 367$) confirmed a reduction in postoperative AKI and need for RRT (0/183 vs. 7/184, $p = 0.015$) [155, 156] (ESM_2 Table S8).

A recent meta-analysis including 15 RCTs in 9623 patients with acute decompensated heart failure showed that the use of BNP (nesiritide) was associated with worsening renal function: RR 1.08 (1.01–1.15), especially in the subgroup receiving a high dose (>0.01 μg/kg/min) and in patients without CKD [157].

In general, most BNP trials were small, not powered for the endpoints RRT or mortality, of poor quality with low fragility index; inclusion criteria varied and results were heterogeneous. Furthermore, hypotension and arrhythmia were frequently reported. A small subgroup meta-analysis on BNP in cardiovascular surgery also showed no benefit [152] (ESM_2 Table S8).

The calcium sensitizer *levosimendan* has inodilator, cardioprotective and anti-inflammatory effects [158, 159]. In a recent meta-analysis of RCTs in the cardiac surgery population (13 trials, 1345 patients), the use of levosimendan decreased the risk of AKI [OR 0.51 (0.24–0.79)], the need for RRT [OR 0.43 (0.25–0.76)] and mortality [OR 0.41 (0.27–0.62)] [160]. The last meta-analysis of RCTs in the critically ill population with or at risk of AKI (33 RCTs, 3867 patients) found that, compared to placebo or another inotrope, levosimendan decreased the risk of AKI [RR 0.79 (0.63–0.99)] and the need for RRT [RR 0.52 (0.32–0.86)]. When limiting the analysis to high-quality studies, the difference in need for RRT between groups failed to reach significance [RR 0.41 (0.15–1.12)] [161]. Studies in both meta-analyses were small, there was some heterogeneity, AKI was not always a predefined endpoint, different definitions of AKI were used and there might have been some outcome reporting bias.

Three large placebo-controlled RCTs have recently been published. In patients with sepsis the use of levosimendan was not beneficial in terms of a reduction of renal SOFA, need for RRT [OR 0.99 (0.66–1.49)] or mortality [OR 1.19 (0.82–1.72)], while its use was associated with more adverse events [162]. In 882 patients with left ventricular dysfunction undergoing cardiac surgery, levosimendan had no effect on mortality or need for RRT [163]. No effect on AKI and RRT was seen when levosimendan was given for haemodynamic support after cardiac surgery in 506 patients [164] (ESM_2 Table S9).

Sedation

Recommendations

1. On the basis of current data no recommendation can be given, although it appears that shorter sedation using propofol or dexmedetomidine may have several advantages, possibly reducing the rate of AKI (BPS).

Rationale

Sedation is necessary in many critically ill patients and this may affect cardiac function and/or vascular tone with renal consequences. In animal models propofol reduced markers of oxidative stress in the kidney [165, 166] and dexmedetomidine caused diuresis through reducing vasopressin secretion, enhancing renal blood flow and hence glomerular filtration [167] and showed renal protection [168–171].

Clinical studies

Propofol is commonly used as anaesthetic and for sedation in the intensive care unit [172]. The "propofol infusion syndrome" comprises myopathy, rhabdomyolysis, hyperkalaemia and AKI [173, 174]. On the basis of the data from case reports/series, it is recommended to administer propofol for a maximum of 48 h and a maximum dose of 4 mg/kg/h [175]. On the other hand, a recent propensity-matched cohort study in critically ill patients showed reduced risk of AKI and need for RRT in patients sedated with propofol as compared to midazolam [176]. Furthermore a small RCT including 112 patients undergoing valvular heart surgery showed less AKI and significantly lower cystatin C levels in the group treated with propofol as compared to sevoflurane [177]. However, the fact that remote ischaemic preconditioning showed less effect if patients were treated with propofol leaves uncertainty about the protective effect of propofol on the kidney [178].

α-2 Adrenergic agonists have multiple pharmacodynamic effects [179]. In a placebo-controlled double-blind RCT *dexmedetomidine* demonstrated significant diuretic effects, with an almost 75% increase in diuresis after cardiac surgery, but did not affect renal function per se [180]. Observational trials indicated protection of kidney function after cardiac surgery [181] but not when used for sedation during lung cancer resection [182]. A placebo-controlled study in 90 patients undergoing coronary artery bypass graft (CABG) showed a dose-dependent reduction of NGAL levels with dexmedetomidine used for postoperative sedation [183]. Another RCT in 200 patients showed that dexmedetomidine for 24 h at 0.4 μg/kg/h from start of anaesthesia resulted in reduced rate of AKI, morbidity and length of stay in the ICU [184] (ESM_2 Table S10).

Alltogether, the data for non-benzodiazepine sedatives, especially dexmedetomidine, are promising but currently not sufficiently convincing to give a clear recommendation.

Hormonal manipulation

Recommendations

1. We *suggest* targeting a blood glucose level at least below 180 mg/dL (10 mmol/l) for the prevention of hyperglycaemic kidney damage in the general ICU population (Grade 2B).
2. We *suggest* not using erythropoietin (Grade 2B) or steroids (Grade 2B) for prevention of acute kidney injury.

Rationale

In critical illness hyperglycaemia has been associated with adverse outcomes [185, 186] attributed to oxidative stress, endothelial dysfunction, alterations in haemostasis, immune dysregulation and mitochondrial dysfunction. The anti-inflammatory effect of steroids may attenuate the inflammatory component of AKI pathogenesis. Erythropoietin (EPO), besides being a haematopoietic growth factor, also has tissue-protective properties by decreasing apoptosis and inflammation and by promoting neovascularization and tissue regeneration.

Clinical studies

A large prospective RCT in 1548 surgical ICU patients compared *tight glucose control (TGC)* with insulin (target blood glucose 80–110 mg/dL) to standard care (insulin when blood glucose is greater than 200 mg/dL resulting in a mean blood glucose of 150–160 mg/dL) and showed not only an improved survival rate but also a 41% reduction in AKI requiring RRT [187]. Additionally, TGC also reduced the number of patients with peak plasma creatinine greater than 2.5 mg/dL by 27%. A subsequent study in the medical ICU of the same hospital, including many patients that already had AKI on admission, did not confirm the effect on survival or need for RRT, but showed a 34% reduction in AKI, defined as a doubling of serum creatinine compared with the admission level [188]. A combined analysis of both studies showed a more pronounced renal protection when normoglycaemia was achieved [189].

More recent RCTs in septic [65] and general [190–194] ICU patients (some of which had to be stopped early because of hypoglycaemia) including a large adequately powered multicentre trial in Australia and New Zealand (NICE-SUGAR) [191] did not confirm the renoprotective effect. The latter even found a higher mortality in patients treated with TGC compared to an intermediate level. Clinicians should, however, be aware of important differences between these landmark trials, such as the glycaemic target in the control group, the nutritional strategy and the methods used to measure blood glucose levels [195]. The most recent meta-analysis on this issue did not find a mortality benefit [RR 1.06 (0.99–1.13)] [196] of TGC nor a renoprotective effect (evaluated by the need for RRT only) [RR 0.96 (0.83–1.11)] [196] (ESM_2 Table S11).

A major obstacle to the broad implementation of TGC is the increased risk of hypoglycaemia. Patients with AKI are at particular risk [197]. On the other hand, a causal relationship between a short-lasting iatrogenic hypoglycaemia in the monitored setting of an ICU and outcome remains controversial [198–200]. If clinicians decide to adopt TGC strategies, fluctuations in glucose levels should be minimized and reliable tools should be employed to measure blood glucose [195]. Because of the risk of hypoglycemia, current guidelines suggest more moderate blood glucose targets (less than 180 mg/dL [20], less than 150 mg/dl [52], 140–180 mg/dL [201]) in critically ill patients, although these targets have not been formally compared with tolerating hyperglycaemia [202] (ESM_2 Table S11).

A recent large RCT ($n = 4494$) demonstrated no significant effect of the intraoperative administration of *dexamethasone* on a composite endpoint of major complications after cardiac surgery. The RR for RIFLE-Failure was 0.7 (0.44–1.14) [203]. A post hoc analysis of this trial showed a beneficial effect on the need for RRT (RR 0.44 (0.19–0.96)), an effect that was mainly seen in patients with eGFR less than 15 ml/min/1.73 m^2 and remains to be confirmed [204]. Another placebo-controlled RCT in 7507 patients found no effect of methylprednisolone on the incidence of AKI stage 3 after cardiac surgery [205].

Prospective randomised placebo-controlled trials on the renoprotective effect of *erythropoietin* have mainly been performed in the setting of cardiac surgery [206–210]. A recent meta-analysis (5 studies, 423 patients) found no effect of erythropoietin on the incidence of AKI: RR 0.64 (0.35–1.16). Surprisingly, a preplanned subgroup analysis found a significant reduction of AKI in patients without high risk for AKI: RR 0.37 (0.24–0.61; $p < 0.0001$) [211]. Similar results were obtained in the most recent meta-analysis, which in addition showed more protection with pre-anaesthetic administration [212]. Another RCT in cardiac surgery including 75 patients with pre-existing renal impairment found no differences in postoperative levels of serum creatinine, cystatin C or NGAL [213]. A second meta-analysis (on a total of 2759 patients) that also included studies in ICU patients [214, 215] likewise did not establish a renoprotective effect of erythropoietin: incidence of AKI RR 0.72 (0.79–1.19); dialysis requirement RR 0.72 (0.31–1.70), mortality RR 0.96 (0.78–1.18), all without significant heterogeneity amongst studies [216]. It should, however, be emphasized that in the largest study in ICU patients [215] AKI was only reported as an adverse effect and not clearly defined. Two more recent RCTs in the setting of

thoracic aortic surgery [217] and contrast administration in diabetics [218] confirmed the absence of beneficial effect of EPO on the incidence of AKI or need for RRT in critically ill patients (ESM_2 Table S12).

Metabolic interventions

Recommendations

1. We *recommend* not using high-dose IV selenium for renal protection in critically ill patients (1B).
2. We *suggest* not using *N*-acetylcysteine to prevent contrast-associated AKI in critically ill patients because of conflicting results and possible adverse effects (Grade 2B).
3. We *suggest* that all patients with or at risk of acute kidney injury have adequate nutritional support preferably through the enteral route (BPS).

Rationale

Starvation accelerates protein breakdown and impairs protein synthesis in the kidney, whereas feeding might exert the opposite effects and promote renal regeneration. In animal experiments increased protein intake has been shown to reduce tubular injury [219, 220], and enteral versus parenteral nutrition improved the resolution of AKI [221]. On the other hand, amino acids infused before or during ischaemia may also enhance tubular damage and accelerate loss of renal function [222]. This may also extend to high-dose glutamine when given to patients during the injury phase of AKI [223]. Furthermore, brief periods of reduced food intake appear to increase resistance against ischaemia–reperfusion injury in rodents [224]. This "amino acid paradox" may be related to the increase in metabolic work for transport processes which may aggravate ischaemic injury. Enhanced autophagy, induced by nutrient deprivation and promoting the repair of cellular damage, may be an alternative explanation. In this context permissive underfeeding during the acute phase of critical illness may be protective against AKI.

One aspect of nutrition is the adequate supply of nutritional co-factors and antioxidants such as the glutathione precursor *N*-acetylcysteine (NAC), antioxidant vitamins (vitamin E (α-tocopherol) and vitamin C (ascorbic acid)) as well as selenium. However, these antioxidants have also been investigated in pharmacological doses with the intention to provide protection against damage by oxygen radicals.

Clinical studies

Protein(s) and amino acids augment renal perfusion and improve renal function, representing recruitment of "renal reserve capacity" [225]. An RCT investigating the effects of daily intravenous amino acid supplementation up to 100 g/day in 424 critically ill patients could not find a significant effect on the duration of AKI despite an increase in eGFR in the treatment group [226]. Furthermore, there was a trend towards increased need for RRT which corresponds to findings from the EPaNIC trial where early parenteral nutrition increased the duration of RRT probably driven by higher urea levels [227]. Correspondingly, lower caloric intake (defined as receiving less than 60% of requirements, also called permissive underfeeding) has been found to be associated with a lower risk for RRT (RR 0.711, 95% CI 0.545–0.928) [228].

A host of RCTs have been performed comparing *NAC* to placebo or other interventions with or without hydration in non-critically ill patients receiving radiocontrast media [229–237]. Results are controversial as alluded to earlier but the latest meta-analysis assessing the efficacy of intravenous NAC only showed no reduction of AKI or RRT [238]. The ACT trial, currently the largest RCT including 2308 patients undergoing coronary and peripheral vascular angiography, failed to demonstrate any beneficial effect of NAC [239]. RCTs in the critically ill population are not available.

RCTs examining the role of NAC in the prevention of renal dysfunction in high-risk contexts like cardiac surgery showed controversial results [240–246] (ESM_2 Table S13). In addition IV NAC may be harmful leading to allergic reactions [247] and decreased cardiac output or survival in patients with septic shock [248, 249].

A small RCT in 42 patients showed that *selenium* supplementation decreased the requirement for RRT from 43% to 14% in patients with SIRS [250]. These finding could, however, not be reproduced in consecutive trials [251] including two larger RCTs involving 249 and 1089 patients with sepsis [252, 253].

Statins

Recommendations

1. We *recommend* against the perioperative use of high-dose statins to prevent postoperative AKI in cardiac surgery (Grade 1A).
2. We *suggest* the short-term use of atorvastatin or rosuvastatin to prevent contrast-associated AKI in high-risk patients undergoing coronary contrast angiography (Grade 2B).

Rationale

The pleiotropic effect of statins, including antioxidant, anti-inflammatory and antithrombotic effects, may contribute to nephroprotection [254].

Clinical studies

Statins may have a beneficial role in high-risk patients exposed to contrast administration for angiography, as suggested by three recent RCTs [255–257]. In a multicentre trial in China, 2998 patients with type 2 diabetes or mild to moderate CKD undergoing coronary or peripheral arterial angiography were randomised to a 5-day course of rosuvastatin versus no statin [255]. The incidence of CA-AKI was significantly lower in those receiving rosuvastatin (2.3% vs. 3.9%, respectively, $p = 0.01$). In a single-centre study [256], 504 statin-naïve patients with acute coronary syndrome (ACS) scheduled to undergo an early invasive strategy were randomised to high-dose rosuvastatin at the time of admission versus treatment with atorvastatin commenced at hospital discharge; 6.7% of patients in the early high-dose statin group developed CA-AKI compared to 15.1% in the control group. The 30-day rate of adverse cardiovascular and renal events was also significantly reduced in the rosuvastatin group (3.6% vs. 7.9%, respectively, $p = 0.036$). An RCT in 410 CKD patients showed less CA-AKI in patients randomised to a single dose of atorvastatin within 24 h before contrast exposure compared to the control group (4.5% vs. 17.8%, $p = 0.005$) [257]. Two more recent RCTs found similar effects of statins in diabetics with CKD [258, 259]. These positive findings were confirmed by several meta-analyses combining studies in patients undergoing coronary angiography [260–263] (ESM_2 Table S14). One of these meta-analyses concluded that short-term, pre-procedural, intensive statin treatment only reduced CA-AKI in ACS patients and recommended further studies in non-ACS patients [264]. This meta-analysis, however, did not include the largest RCT [255]. Although, these results lend support to the short-term use of statins before procedures involving intra-arterial contrast exposure in patients with coronary artery disease with or without diabetes and/or CKD, it must be considered that most of the studies were performed outside the ICU, thereby warranting downgrading of the level of evidence.

In patients undergoing cardiac surgery, two large meta-analyses including data from observational studies found conflicting evidence regarding the role of preoperatve statin in preventing postoperative AKI [265, 266], and a Cochrane analysis of small RCTs found no effect [267]. Two recent placebo-controlled RCTs investigated the effects of perioperative high-dose atorvastatin (i.e. 80 mg, followed by 40 mg daily) in elective cardiac surgery [268] and valvular heart surgery [269] and showed no renal benefit. Furthermore, in the largest trial, statin-naïve patients with CKD had a higher incidence of AKI when treated with statin [268] (ESM_2 Table S15). Finally, an even larger placebo-controlled RCT in 1922 cardiac surgery patients that included AKI as a secondary outcome demonstrated renal harm in those receiving rosuvastatin 20 mg/day in the perioperative period [270].

Remote ischaemic preconditioning

Recommendations

1. We *suggest* not using remote ischaemic preconditioning for prevention of AKI in critically ill patients (Grade 2A).

Rationale

Remote ischaemic preconditioning (RIPC) or several short cycles of limb ischaemia is achieved through inflation of a blood pressure cuff. The mechanism by which RIPC prevents AKI is incompletely understood.

Clinical studies

In cardiac surgery several single-centre RCTs demonstrated reduced incidence of AKI and need for RRT [271–273]. However, several others, including four larger and multicentric RCTs [274–277] did not confirm these beneficial effects, nor was a change in creatinine or mortality demonstrated. The conflicting results in cardiac surgery may be explained by inclusion of low-risk patients in trials that showed no benefit, and the use of propofol and opioids, treatments that may blunt the beneficial effects of RIPC.

In 13 recent meta-analyses the effect of RIPC was evaluated in different cohorts and definitions of AKI [178, 278–289]. Though several meta-analyses found a reduction of AKI [278, 279, 281–284, 286, 287, 289, 290] this was restricted to stage 1 AKI [289], or subgroups such as percutaneous coronary interventions [278, 279], or cardiac surgery with propofol-free anaesthesia [283]. The meta-analyses are limited by risk of bias, heterogeneity in definitions of AKI, low event rates and underestimation of influence of co-morbidities [283, 289]. Finally, a Cochrane review including studies on patients undergoing surgery could not show a benefit on renal outcomes [178] (ESM_2 Table S16).

In summary, the effects by which RIPC prevents AKI are incompletely understood. RIPC for prevention of AKI has mainly been evaluated in cardiovascular surgery and after contrast administration. Larger studies and meta-analyses are not consistent in demonstrating a preventive effect of RIPC for AKI.

AKI care bundles

Recommendations

1. We *suggest* using the KDIGO recommendations to reduce the incidence of AKI after cardiac surgery (Grade 2C).
2. The use of AKI care bundles outside the intensive care unit has some benefits, including the potential to improve the outcome of AKI (BPS).

Rationale

Care bundles have been proposed as tools to improve the quality of care and outcome of patients with AKI. Ideally, they should contain a small set of practices, processes or treatments that are evidence-based, endorsed and/or recommended by guidelines and broadly accepted as appropriate and/or standard care by local stakeholders. They are designed such that if one element is not implemented, the remaining elements are not impacted.

Clinical studies

Outside the critical care setting, different AKI care bundles have been implemented with variable improvement in clinical care, more efficient resource use and potentially improved outcomes, especially if combined with educational measures and electronic alerting [291–293]. To date, care bundles comprising the KDIGO recommendations have only been investigated in one study including 274 cardiac surgery patients at high risk for AKI as determined by AKI biomarkers. The study showed less postoperative AKI (although mainly by the urine output criteria) without, however, influencing any major patient-centred outcome like RRT or renal recovery at day 30 [294]. The treatment strategy included avoidance of nephrotoxins and hyperglycaemia as well as applying goal-directed haemodynamic optimisation. It is unclear which element was effective because goal-directed therapy (GDT) neither prevented AKI nor reduced the need for RRT in septic shock, as shown by a secondary analysis [23] and a meta-analysis of three recent large RCTs [295], but avoiding nephrotoxins, hyperglycaemia and hypovolaemia seems to be reasonable.

Conclusions and summary

Prompt resuscitation of the circulation with fluids, vasopressors and inotropes remains the cornerstone in the prevention of AKI. Volume expansion with isotonic crystalloids is only recommended in states of true and suspected hypovolaemia. Uncontrolled volume expansion and the use of starches and dextrans should be avoided. Following or together with fluid resuscitation hypotensive patients should be given a vasoconstrictor, preferably norepinephrine, and titrated individually with a target MAP of 65–70 mmHg being adequate in most individuals without pre-existing chronic hypertension. The potential role of vasopressin requires further investigation. Together with these measures a review of all medications with the cessation of those known to be nephrotoxic is mandatory. Diuretics should not be used for prevention of AKI alone but may benefit the kidney by relieving renal congestion. Frank hyperglycaemia should be avoided. The effect of statins appears to depend on the setting, with promising results in contrast administration but no effect or even harm in cardiac surgery. There is low-level evidence that the choice of the sedative may impact kidney function. The conflicting results on ischaemic preconditioning preclude a firm recommendation.

Heterogeneous definitions of AKI still hamper comparison of different studies, despite the commendable efforts by the ADQI, AKIN and KDIGO working groups [2, 296, 297]. In addition, AKI is frequently reported as a secondary outcome. Although several RCTs have fuelled the literature on prevention of AKI over the past 4–5 years, the available evidence remains insufficient. Many recommendations are therefore formulated as weak with low grade quality of evidence. More high-quality studies with consensus AKI definitions will be required to fill the knowledge gaps.

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Compliance with ethical standards

Conflicts of interest
MJ has received honoraria or research support from Baxter Healthcare Corp, AM-Pharma, CLS Behring, Fresenius and Astute Medical. WD declares no conflicts of interest. LF has received honoraria and research support from Astute Medical, Fresenius, Baxter Gambro Renal and Orthoclinical Diagnostics. PH had received research grants from Baxter, AM Pharma, Bellco, and Pfizer EH received speaker's fees from Alexion and Astute Medical, and a research grant from Bellco. MO has received honoraria and research funding from Fresenius Medical Care and Baxter Gambro. HO has financial congress support from Dirinco (Netherlands) and speaker's honoraria from Fresenius and Gambro/Baxter. MS declares no conflicts of interest.

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