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EDITORIAL

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Clinical guidelines for the protection of kidney function and prevention of acute kidney injury in the intensive care unit: common sense rather than magic bullets?

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The incidence of acute kidney injury (AKI) during hospital admission continues to rise in the developed world [1]. Typically, AKI occurs in a multi-factorial setting, more commonly affecting the older patient, with a background of pre-existing chronic kidney disease (CKD), and may be a reflection of both underlying patient co-morbidities and the increasing number and complexity of therapeutic options now available as medical technology continually advances. Not only does the development of AKI increase in-hospital mortality, but it also lengthens hospital in-patient stay, with increased health-care costs. More recent studies have now shown that the survivors have reduced short-term survival following hospital discharge, but also an increased risk of developing progressive CKD, which may subsequently require chronic dialysis treatment in the longer term [2].

It is therefore timely that Joannidis and colleagues [3] have performed an extensive literature search and using the GRADE scoring system [4, 5] have proposed a series of clinical guidelines designed to help prevent AKI and protect kidney function in patients in the intensive care unit (ICU). The purpose of clinical guidelines is to help clinicians provide the best evidence-based patient care, but they also aid governmental health care policy makers, health care providers and insurers, patients and medical litigation lawyers by providing a benchmark standard of practice [6]. In addition, clinical guidelines help identify gaps in evidence that can then direct researchers and medical scientific research funding agencies. To achieve their goal, clinical guidelines must meet three key quality standards: well conceived with a defined scope and purpose, systematic review of the relevant primary literature, with transparent search strategies, providing criteria for both study inclusion and exclusion, and finally careful and detailed assessment of the quality of evidence [7].

The authors defined the scope of their guidelines and thereby deliberately excluded AKI associated with transplantation, primary renal disease and hepatorenal failure. In addition, although not formerly excluded, they did not consider the potential role of raised intra-abdominal pressure, ventilatory practices, blood transfusion or nephrotoxic drugs in causing AKI, and also did not fully address the cardiorenal syndromes.

It is only relatively recently that there has been a consensus on the definition of AKI, initially proposed by the ADQI group [8], which was then further revised by the AKI network, to define the timeframe of "acute" [9]. Thus, any literature search would have reviewed many publications with widely differing definitions of AKI, and this would have been compounded in the ICU setting, where the majority of patients are started on renal replacement therapy to correct volume overload [10] and/or acidosis rather than for azotaemia. Ideally, any intervention that can prevent AKI or protect kidney function should be readily reproducible in prospective multicenter trials. As with any literature review, not all studies were primary randomized controlled clinical trials [11], and similarly only a minority were conducted specifically within the ICU setting, and so the question

arises as to whether the results of studies undertaken outside the ICU are directly applicable to those patients within the ICU.

At times, the authors step outside their defined scope of prevention of AKI and protecting kidney function in the ICU by extending their guidelines to patients undergoing cardiac surgery. This may have been due to a lack of appropriate studies in the ICU setting. For example, in the section on vasodilators, Joannidis and colleagues make a weak recommendation by suggesting the prophylactic use of fenoldopam for cardiac surgery patients at risk of AKI. However, the authors need to consider whether their guideline recommendations may be taken out of context from their specific recommendation and become generalized to the ICU patient without the appropriate level of evidence. As a therapeutic intervention that may be useful in reducing the incidence of AKI, for example, during cardiac surgery, may not necessarily be equally effective for other causes of AKI, such as sepsis.

The authors stress the importance of appropriate fluid resuscitation prior to the administration of contrast nephropathy, and maintaining sodium driven diuresis, but also advocate the use of peri-procedural hemofiltration in patients with severe chronic kidney disease undergoing coronary intervention, based on a limited experience. Although again this may appear to have strayed outside their intensive care remit, they do not review the literature on the risk of radiocontrast-induced nephropathy [12], which is often multi-factorial, related to the total dose of contrast administered, the route of administration, the type of contrast agent (hyperosmolar, iso-osmolar or hypo-osmolar, and ionic charge), and time interval between examinations. There are guidelines published by the European Society of Urogenital Radiology, again designed to reduce the risk of contrast nephropathy [13]. It is therefore important that when specialist societies construct their own clinical practice guidelines that they are cognizant of prior publications from other specialist groups with overlapping clinical practices to provide consistency were possible rather than diversity.

Joannidis and colleagues should be congratulated for their timely efforts. They have undertaken an extensive review and critique of the currently available literature. However, their clinical practice guidelines could potentially have benefited from a more systematic evidenced-based approach with limited but clearly defined and focused clinical questions. Their review has highlighted several areas of clinical uncertainty because of the lack of appropriately powered primary studies, and this needs to be emphasized so that these gaps in medical knowledge can be filled by future adequately powered multi-center prospective studies.

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

Expert opinion of the working group for nephrology, ESICM

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Abstract *Background:* Acute renal failure on the intensive care unit is associated with significant mortality and morbidity. *Objectives:* To determine recommendations for the prevention of acute kidney injury (AKI), focusing on the role of potential preventative maneuvers including volume expansion, diuretics, use of inotropes, vasopressors/vasodilators, hormonal interventions, nutrition, and extracorporeal techniques. *Method:* A systematic search of the literature was performed for studies using these potential protective agents in adult patients at risk for acute renal failure/kidney injury between 1966 and 2009. The following clinical conditions were considered: major surgery, critical illness, sepsis, shock, and use of potentially nephrotoxic drugs and radiocontrast media. Where possible the following endpoints were extracted: creatinine clearance, glomerular filtration rate, increase in serum creatinine, urine output, and markers of tubular injury. Clinical endpoints included the need for renal replacement therapy, length of stay, and mortality. Studies are graded according to the international Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) group system *Conclusions and recommendations:* Several measures are recommended, though none carries grade 1A. We recommend prompt resuscitation of the circulation with special attention to providing adequate hydration whilst avoiding high-molecular-weight hydroxy-ethyl starch (HES) preparations, maintaining adequate blood

pressure using vasopressors in vasodilatory shock. We suggest using vasopressors in vasodilatory hypotension, specific vasodilators under strict hemodynamic control, sodium bicarbonate for emergency procedures administering contrast media, and periprocedural hemofiltration in severe chronic renal insufficiency undergoing coronary intervention.

Keywords Acute kidney injury · Systematic review · Recommendations · Position paper · Prevention · Volume expansion · Vasopressors · Vasodilators · Diuretics · Hormones · APC · Renal replacement therapy

Introduction

Acute kidney injury (AKI) often complicates the course of critical illness and, although previously considered as a marker rather than a cause of adverse outcomes, it is now known to the extent possible to be independently associated with an increase in both morbidity and mortality [1–11]. The major causes of AKI in the intensive care unit (ICU) include renal hypoperfusion, sepsis/systemic inflammatory response syndrome (SIRS), and direct nephrotoxicity, although in most cases etiology is multifactorial [12–15]. Furthermore, epidemiological studies involving patients undergoing cardiothoracic surgery [16, 17] or contrast administration [18, 19] have determined additional risk factors including age, preexisting hypertension, diabetes mellitus, heart failure, and prolonged and complex surgery. It follows that minimizing renal injury should confer a benefit to patients.

This review is the result of an international collaboration of the Critical Care Nephrology Working Group of the European Society of Intensive Care Medicine (ESICM) with the principal aim of providing a critical evaluation of available evidence and to give recommendations, where possible, for clinical practice. We have focused primarily on the role of volume expansion, diuretics, inotropes, vasopressors/vasodilators, hormonal interventions, nutrition, and extracorporeal techniques, which are the major interventions routinely and easily undertaken in intensive care practice.

Methods

A systematic search of the literature was performed using the following databases: Medline (1966 through 2009, April), Embase (1980 through 2009, week 15), CINAHL (1982 through 2009, April), Web of Science (1955 through 2009), and PubMed/PubMed Central to identify key studies, preferably randomized placebo-controlled trials (RCT) and meta-analyses, on AKI/acute renal failure (ARF) addressing the use of therapeutic strategies to prevent renal dysfunction in adult critically ill patients. The following clinical conditions were considered: major surgery, critical illness, sepsis, shock, and use of potentially nephrotoxic drugs and radiocontrast. Transplantation, primary renal disease (e.g., vasculitis), and the hepatorenal syndrome were not considered.

Search terms and text words are available in electronic supplementary material (ESM), as are the endpoints extracted.

These recommendations are intended to provide guidance for the clinician caring for a patient at risk of AKI. The process of developing these recommendations included a modified Delphi process, three nominal consensus conferences during the annual meetings of the European Society of Intensive Care Medicine 2005 and 2006, followed by electronic-based discussions. The quality of the evidence was judged by predefined Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria, which has also been employed in developing the latest *Surviving Sepsis* international guidelines [20]. This allows the development and grading of management recommendations through rating the quality of available evidence and grading strength of recommendations in clinical practice, as described in more detail elsewhere [21].

According to the GRADE system the strength of the recommendations is classified as either strong (1) or weak (2) [22]. A strong recommendation (1) indicates that an intervention's desirable effects clearly outweigh undesirable effects such as risk, cost, and other burdens. Weak recommendations (i.e., suggestions) (2) indicate that the balance between undesirable and desirable effects is less clear.

The degree (i.e., quality) of evidence for the recommendations is classified from high (A) to low (C) according to factors including study design, consistency of the results, and directness of the evidence [22]. We regarded repeated large RCTs including $\geq$50 patients in each arm and meta-analyses showing low heterogeneity as providing a high degree of evidence (A) and smaller RCTs or larger RCTs whose results could not be reproduced as providing lower-grade evidence (B). For clinical decision-making, the grade of recommendation is considered of greatest *clinical* importance. It should, however, be emphasized that there may be circumstances in which a recommendation cannot or should not be followed for an individual patient. Furthermore, interventions are generally investigated separately, 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.

Volume expansion

Recommendations

1. We **recommend** controlled fluid resuscitation in true or suspected volume depletion (grade 1C).
2. There is little evidence-based support for the preferential use of crystalloids, human serum albumin, gelatine-derived colloids or the lowest-molecular-weight hydroxy-ethyl starches (HES) for renal protection as long as derangements of serum electrolytes are prevented.
3. We **recommend** avoiding 10% HES 250/0.5 (grade 1B) as well as higher-molecular-weight preparations of HES and dextrans in sepsis (grade 2C).
4. We **recommend** prophylactic volume expansion by isotonic crystalloids in patients at risk of contrast nephropathy (grade 1B). We **suggest** using isotonic sodium bicarbonate solution, especially for emergency procedures (grade 2B).
5. We **suggest** prophylactic volume expansion with crystalloids to prevent AKI by certain drugs (specified below) (grade 2C).

Rationale

Both relative and overt hypovolemia are significant risk factors for the development of AKI [23–26]. Consequently, timely fluid administration is a preventive measure which should be effective both through restoration of circulating volume and minimizing drug-induced nephrotoxicity [27]. Where volume replacement is indicated, this should be performed in a controlled fashion directed by hemodynamic monitoring, as injudicious use of fluids carries its own inherent risk [26]. In the ICU patient this may manifest in several ways, including prolonged mechanical ventilation [28] or the development of intra-abdominal hypertension, which itself is a risk factor for AKI [29].

Volume replacement may employ 5% glucose (i.e., free water), crystalloids (isotonic, half-isotonic), colloids, or more commonly in clinical practice, a combination thereof. Glucose solutions substitute free water and are used to correct hyperosmolar states, although the mainstay for correction of extracellular volume depletion remains isotonic crystalloids. However, the increased chloride load may result in hyperchloremic acidosis and associated renal vasoconstriction as well as altered perfusion of other organs such as the gut [30]. Crystalloids expand plasma volume by approximately 25% of the infused volume, whereas colloid infusion results in a greater expansion of plasma volume. The degree of expansion is dependent on concentration, mean molecular weight, and (for HES) the degree of molecular substitution. However, large-volume replacement with colloids in isolation risks hyperoncotic impairment of glomerular filtration [31, 32] as well as osmotic tubular damage, particularly in sepsis [33–35].

Commonly employed colloids include human albumin (HA), gelatins, dextranes, and HES. HA may appear attractive in hypooncotic hypovolemia but is costly [36–38]. A large multicenter RCT comparing 4% albumin with crystalloid failed to demonstrate any difference in outcome parameters including renal function, but proved that albumin itself was safe [39]. Gelatines have an average molecular weight of ca. 30 kDa, and the observed intravascular volume effect is shorter than that observed with HA or HES. Advantages include the lack of deleterious effects on renal function [40, 41] offset by the possibility of prion transmission, histamine release, and coagulation problems, particularly if large volumes are infused [42, 43]. Dextrans are single-chain polysaccharides comparable to albumin in size (40–70 kDa) and with a reasonably high volume effect, although anaphylaxis, coagulation disorders, and indeed AKI may occur at doses higher than 1.5 g/(kg day) [44–47]. HES are highly polymerized sugar molecules characterized by molecular weight, grade of substitution, concentration, and C2/C6 ratio. Their volume effect is greater than that of albumin, especially when larger-sized polymers are employed which degrade through hydrolytic cleavage the products of which undergo renal elimination. These degradation products may be reabsorbed and contribute to osmotic nephrosis and possibly medullary hypoxia [35, 48]. A further problem with HES may be tissue deposition and associated pruritus, which appears to be dose dependent [49–51]. These adverse effects may be less pronounced in the more modern, rapidly degradable HES solutions such as HES 130/0.4 [52–54].

Clinical studies

Unsurprisingly, no studies have specifically addressed the effects of volume expansion in overt hypovolemia compared with no volume resuscitation given the intuitive benefits of volume replacement. A large prospective observational trial of the CRYCO (CRYstalloids or COlloids?) study group found an increased risk of AKI in 1,013 ICU patients with shock receiving either hyperoncotic artificial colloids or albumin as compared with crystalloids [55]. This is in contrast to the results of a large RCT comparing isotonic sodium chloride to human serum albumin in various clinical settings, where no differences in renal function were demonstrated [39] (ESM Table S1). Given the lack of a marked beneficial effect the use of albumin should be limited given its expense.

Small studies performed in the perioperative setting have compared a variety of fluid replacement regimes (mainly between various forms of HES, or HES versus

gelatine or albumin) with no definitive conclusions [56–60]. Only one RCT reported better preserved early postoperative renal function with 6% HES 130/0.4 than with 4% gelatine following cardiac surgery [61].

In patients undergoing low-risk surgery with normal renal function, a small RCT comparing lactated Ringers' solution to three different forms of HES demonstrated no adverse effects of either solution [62].

In severe sepsis the beneficial effects of timely volume replacement on organ failure and mortality are well known and are a cornerstone of the *Surviving Sepsis* campaign guidelines [20, 63]. A single-center RCT comparing 5% HA with gelatine in ICU patients showed no difference in renal function despite significant differences in serum albumin levels [64]. A study comparing 6% HES 200/0.5 with gelatine in ICU patients with sepsis demonstrated slightly lower serum creatinine levels in the group receiving gelatine, but no effect was observed on endpoints such as the need for renal replacement therapy (RRT) or mortality [41] (ESM Table S1). However, a large German RCT in patients with septic shock (the VISEP trial) showed a higher incidence of AKI, requirement for RRT, and mortality in the group treated with 10% HES 200/0.5 compared with Ringer's lactate [65]. Adverse effects on renal function may be restricted to higher-molecular-weight HES, as a multivariate analysis in a large European multicenter observational study was unable to detect HES as an independent risk factor, neither in 1,970 ICU patients requiring RRT nor in a subgroup of 822 patients with severe sepsis [66].

Prophylactic volume expansion has been investigated extensively in the setting of contrast-induced nephropathy (CIN) [67–72]. The benefit of this measure has been mainly shown for patients with inherent risk factors of CIN such as reduced glomerular filtration rate (GFR) (<50 ml/min/1.73 m^2), heart failure or diabetes characterized by various risk scores (e.g., Thakar score [18] or Mehran score [19]). The first RCT comparing protection in CIN by half normal saline versus half normal saline plus diuretic therapy clearly demonstrated the superiority of volume expansion by half normal saline at a rate of 1 ml/kg 12 h before and after angiography [67]. However, a larger RCT including 1,620 patients undergoing coronary angioplasty showed a lower incidence of CIN when using normal saline compared with half normal saline [68]. Given that normal saline contains a high amount of chloride, the protective effect of isotonic bicarbonate solutions (containing 150–154 mmol/l sodium) in patients with impaired renal function receiving contrast agents has been studied. This showed a significant reduction in the incidence of CIN [69–75], but not in the need of renal replacement therapy or mortality. Most investigations applied a hydration regimen starting at 3(–5) ml/(kg h) 1 h before radiocontrast application, followed by 1 ml/(kg h) for at least 6 h post procedure [69, 71–73, 75]. Although three recent RCTs indicated that hydration with saline or sodium bicarbonate were equally effective [76–78], when included in meta-analyses a benefit of sodium bicarbonate over normal saline could still be detected [74, 79–81] (ESM Table S2). In a recent RCT of cardiac surgical patients at risk for AKI, intravenous sodium bicarbonate was associated with a lower incidence of acute renal dysfunction [82]. Nevertheless, adequately powered RCTs are still needed to determine whether sodium bicarbonate will reduce clinically meaningful outcomes.

Hypovolemia may also contribute significantly towards drug-induced renal injury, although the available evidence supporting preventative hydration is observational with no consensus found as to the timing, optimal volume, and type of solution to be employed [12]. Prevention of nephrotoxicity through prophylactic volume expansion has been shown to be of benefit with amphotericin B, antivirals including foscarnet, cidofovir, and adefovir [83–85], as well as drugs causing crystal nephropathy such as indinavir, acyclovir, and sulfadiazine [86].

Diuretics

Recommendations

1. We **recommend** that loop diuretics are not used to prevent or ameliorate AKI (grade 1B).

Rationale

Oligo-anuria frequently is the first indicator of acute renal dysfunction. A multinational survey has demonstrated that 70% of intensivists used loop diuretics in a wide spectrum of AKI settings [87]. There may indeed be some theoretical attractions in using diuretics to ameliorate AKI, including prevention of tubular obstruction, reduction in medullary oxygen consumption, and increase in renal blood flow [88–90].

Clinical studies

Few prospective randomized trials have addressed the role of diuretics in the prevention of AKI. Most of the available studies have been done in the setting of contrast administration [67, 91, 92] and cardiac surgery [93, 94]. No protection against contrast nephropathy has been observed with diuretics, and in cardiac surgery, higher postoperative serum creatinine levels were found in patients receiving furosemide [93, 94].

To date four randomized controlled trials have examined the role of diuretics in *established* renal failure in the intensive care setting. No demonstrable improvement in primary outcome parameters, such as recovery of renal function or mortality, has been observed [35, 95–97]. Other studies have compared diuretics with dopamine or against placebo, again with no perceived benefit [33, 98, 99]. Three meta-analyses confirmed that the use of diuretics in established AKI does not alter outcome but carries a significant risk of side-effects such as hearing loss [100–102] (ESM Table S3). Furthermore, in an international cohort study an increase in the risk of death or an increase in established renal failure was observed. These findings, however, could not be confirmed in a second cohort study [103, 104].

Vasopressors and inotropes

Recommendations

1. We **recommend** that mean arterial pressure (MAP) be maintained ≥60–65 mmHg (grade 1C), however, target pressure should be individualized where possible, especially if knowledge of the premorbid blood pressure is available.
2. In case of vasoplegic hypotension as a result of sepsis or SIRS we **recommend** either norepinephrine or dopamine (along with fluid resuscitation) as the first-choice vasopressor agent to correct hypotension (grade 1C).
3. We **recommend** that low-dose dopamine not be used for protection against AKI (grade 1A).

Rationale

Preservation or improvement of renal perfusion can theoretically be achieved by fluid resuscitation, through renal vasodilators, by systemic vasopressors that redirect blood flow to the kidney or by increasing cardiac output through the use of inotropic drugs. Whereas a recent study indicated that any MAP of ≥60 mmHg may be considered adequate for patients with septic shock [105], additional benefits with regards to renal function were not observed when a target MAP of more than 85 mmHg was compared to a target of 65 mmHg [106]. However, it must be borne in mind that this study may not be widely applicable to the patients admitted to the intensive care unit with pre-existing comorbidities. Those at greatest risk of developing AKI include those patients with vascular disease, hypertension, diabetes, increased age, and elevated intra-abdominal pressure, for whom the target mean arterial pressures may have to be individually tailored.

Clinical studies

Low-dose or "renal-dose" dopamine has been advocated in the past to prevent selective renal vasoconstriction in a variety of conditions [107]. Although dopamine infusion may improve renal perfusion in healthy volunteers, no improvement of renal perfusion nor preventive benefit with respect to renal dysfunction has been unequivocally demonstrated in the critically ill, where increased sympathetic activity and local norepinephrine release may contribute to renal vasoconstriction [108–110]. Dopamine also has an inotropic effect, but observed increases in diuresis or even a reduction in serum creatinine during dopamine infusion does not protect against AKI [107, 110, 111]. Several meta-analyses have concluded that "renal-dose" dopamine is of no benefit in either preventing or ameliorating AKI in the critically ill and may even promote AKI [107, 109, 112].

The inotropic agents dobutamine and dopexamine have also been examined, but to date no prospective controlled clinical trial has demonstrated a protective effect on renal function [113]. In contrast, the effect of dobutamine on renal function is variable, even when favorably affecting cardiac output [111].

Norepinephrine is known to be of use in the treatment of vasodilatory shock after adequate fluid loading. In nonrandomized studies, administration of norepinephrine and resulting increases in arterial blood pressure have shown to increase diuresis and creatinine clearance [114]. Whether this is due to increased renal perfusion and thus implies renal protection is unknown. A RCT on 252 adult patients comparing dopamine in septic shock with norepinephrine as the initial vasopressor showed no significant differences between groups with regard to renal function or mortality. Though norepinephrine was associated with significantly less sinus tachycardia and arrhythmias (Patel GP et al., Shock, in press).

Vasopressin is gaining popularity in the treatment of norepinephrine-refractory shock [115] increasing blood pressure and enhancing diuresis in hypotensive oliguric patients but as yet has not been proven to enhance survival nor to prevent or ameliorate AKI in the critically ill [116].

Vasodilators

Recommendations

1. We **suggest** using vasodilators for renal protection when volume status is corrected and the patient is closely hemodynamically monitored with particular regard to the development of hypotension (grade 2C). When choosing a vasodilator, the clinical condition of the patient, the availability of the drug, and the concomitant interventions should be considered.

2. We **suggest** the prophylactic use of fenoldopam, if available, in cardiovascular surgery patients at risk of AKI (grade 2B). We **recommend** that fenoldopam is not used for prophylaxis of contrast nephropathy (grade 1A).
3. We **suggest** using theophylline to minimize risk of contrast nephropathy, especially in acute interventions (grade 2C) when hydration is not feasible.
4. We **suggest** that natriuretic peptides are not used as protective agents against AKI in critically ill patients (grade 2B), while its use may be considered during cardiovascular surgery (grade 2B).

Rationale

Reduced tissue perfusion elicits neurohumoral activation leading to increased sympathetic tone, endothelin production, and activation of the renin–angiotensin–aldosterone system which maintains systemic blood pressure often at the cost of both splanchnic and renal vasoconstriction. Glomerular perfusion and filtration pressure are maintained through afferent arteriolar vasodilatation and efferent vasoconstriction, but once these compensatory mechanisms fail, a decline in glomerular filtration ensues. This critical threshold for renal perfusion depends on the ability of compensatory intrarenal vasodilatation. It is increased, for example, with chronic hypertension and high venous pressure states and decreased by endogenous or exogenous vasodilators [117–121]. In circumstances of persistent renal vasoconstriction, vasodilators might have a beneficial effect on kidney function. However, the use of vasodilators may cause hypotension by counteracting compensatory vasoconstriction, thus unmasking occult hypovolemia, and as such the correction of hypovolemia is crucial.

Clinical studies

Fenoldopam is a pure dopamine A-1 receptor agonist. Three RCTs have evaluated the effects of continuous infusion of fenoldopam on renal function in critically ill patients with AKI and observed mixed results [122–124]. Two compared fenoldopam with placebo, and one with dopamine. In one, fenoldopam was found to be beneficial with regard to the primary endpoints of dialysis-free survival at 21 days and need of RRT in the selected subgroups of patients without "diabetes mellitus" or "after cardiac surgery" [124]. In another, fenoldopam caused a significant decrease in mild AKI (defined as a rise in serum creatinine >150 μmol/L) and ICU stay, and a nonsignificant decrease in severe AKI (serum creatinine >300 μmol/L) [123]. In the third, infusion of fenoldopam, but not dopamine, over 4 days significantly reduced serum creatinine [122]. Prophylactic administration of fenoldopam has been studied during surgery and following administration of radiocontrast. A meta-analysis including 1,059 patients undergoing cardiovascular surgery found that fenoldopam consistently and significantly reduced the need for RRT and in-hospital mortality [125]. A second meta-analysis including 1,290 critically ill and surgical patients from 16 randomized studies reported that the use of fenoldopam reduced the incidence of acute renal injury, need for RRT, and hospital mortality [126]. However, none of the larger RCTs showed that using fenoldopam for the prevention of contrast nephropathy confers renal protection [127, 128] (studies summarized in ESM Table S4).

Clonidine is a central and peripheral adrenergic-receptor blocking agent with predominantly $\alpha 2$ blocking effects which also reduces plasma renin levels. Two RCTs, again involving cardiothoracic patients demonstrated some beneficial effects of clonidine on renal function [129, 130]. However, the use of β-blockers as part of current practice is not mentioned in these studies (ESM Table S5).

Anaritide (ANP) is produced by cardiac atria in response to atrial dilatation and induces afferent glomerular dilatation and efferent vasoconstriction as well as increasing urinary sodium excretion, renal blood flow, and GFR in early ischemic AKI with a dose-dependent hypotensive effect [131]. Ularitide and nesiritide (brain natriuretic peptide, BNP) have similar effects. The first large RCT evaluating ANP in AKI found a reduction of RRT in the oliguric subgroup only [132]. Disappointing results were subsequently observed in RCTs of anaritide and ularitide in patients with oliguric AKI [133–135]. In contrast, a RCT in post cardiac surgery patients with heart failure and early renal dysfunction demonstrated that use of continuous low-dose anaritide significantly reduced the need for RRT [136]. The effect of nesiritide was even more pronounced in cardiac surgery patients with reduced ejection fraction (NAPA trial), demonstrating shorter hospital stay and reduced 180-day mortality [137]. The observed differences might be explained by differences in dose and duration of drug administration with a consequent reduction in hypotension observed. Similarly, protective effects on renal function were observed with low-dose nesiritide in elective abdominal aneurysm repair [138] and in cardiac bypass surgery [139]. Of note, a recent meta-analysis comparing non-inotrope-based treatment with nesiritide (h-BNP) therapy indicated that this may be associated with an increased risk of renal failure and death in a select population of patients with acutely decompensated heart failure [140] (ESM Table S6).

Phosphodiesterase (PDE) inhibitors have both vasodilatory and inotropic effects and modulate the inflammatory response, rendering them interesting candidates for the prevention of renal damage. Ten controlled trials evaluating the effect of theophylline on the

prevention of contrast nephropathy showed varying efficacy in attenuating increases in serum creatinine after administration of radiocontrast media [141–151]. The results of three successive meta-analyses remained inconclusive [142, 147, 152]. However, a more recent trial has demonstrated a reduction in the incidence of contrast nephropathy by preprocedural administration of 200 mg theophylline in critically ill patients [151]. Anticipated adverse events such as arrhythmias were not observed (ESM Table S7).

Pentoxifylline has been examined in low risk cardiothoracic patients with no benefit [153] but other small studies examined populations at higher risk and demonstrated beneficial effects on both preservation of renal function and clinical outcomes [154, 155].

Enoximone is a selective phosphodiesterase III inhibitor with both vasodilatory and anti-inflammatory properties. Two small studies in cardiac surgery have evaluated the effect of enoximone, with one study combining enoximone with the β-blocker esmolol [156, 157]. Both demonstrated a reduction in post-bypass inflammation and renal protective effects, although the studies were not designed to show effects on clinical outcomes.

A new phosphodiesterase inhibitor with myocardial calcium sensitizer activity, levosimendan, has recently been approved for the treatment of congestive cardiac failure. A small RCT in 80 patients with acute decompensated heart failure demonstrated short-term improvement of renal function as measured by eGFR which could not be achieved by dobutamine alone [158].

The compensatory release of the vasodilator prostaglandin PGE_1 contributes to the maintenance of renal perfusion through dilatation of both the afferent arteriole and medullary vessels in renal hypoperfusion. Three clinical studies showed a mild protective effect of vasodilator prostaglandins (PGE_1/PGI_2) [159–161].

Angiotensin blockade may have renal protective effects in the acute setting; for example, angiotensin blockade augments renal cortical microvascular PO_2 [162] and restores endothelial dysfunction [163]. Two studies evaluating the effect of short-term intravenous enalaprilat in a cardiac surgical population with poor cardiac function demonstrated improved cardiac and renal function [164, 165].

Hormonal manipulation and activated protein C

Recommendations

1. We **recommend** against the routine use of tight glycemic control in the general ICU population (grade 1A). We **suggest** "normal for age" glycemic control with intravenous (IV) insulin therapy to prevent AKI in surgical ICU patients (grade 2C), on condition that it can be done adequately and safely applying a local protocol which has proven efficacy in minimizing rate of hypoglycemia.
2. We **suggest** not to use thyroxine (grade 2C), erythropoietin (grade 2C), activated protein C (grade 2C) or steroids (grade 2C) routinely to prevent AKI.

Rationale

The effects of blood glucose control with insulin on the development or progression of nephropathy in patients with type I and type II diabetes is well documented [166]. In animal models, insulin-like growth factor 1 (IGF-1) has been shown to accelerate recovery from ischemic and cisplatin-induced AKI [167–169], through either renal hemodynamic actions or through a direct metabolic, mitogenic, and antiapoptotic effect on injured tubular cells. Thyroid hormone has also been seen to accelerate renal recovery in various animal models of AKI [170, 171]. There is increasing experimental evidence from ischemia/reperfusion models that erythropoietin (EPO) reduces apoptotic cell death and induces tubular proliferation [172–175]. A retrospective clinical study also showed a slowing of the progression of chronic renal failure in predialysis patients [176]. However, erythropoietin in high doses may induce renal vasoconstriction, systemic hypertension, increase the risk of thrombosis, and increase tumor burden, limiting clinical applicability [177]. New derivatives of EPO that are devoid of hematopoietic activity may be safer [178].

Activated protein C (APC) has pleiotropic actions including anticoagulation, profibrinolysis, anti-inflammation, and antiapoptosis activity, and may therefore be an ideal candidate to prevent ischemia/reperfusion-induced organ failure. Indeed, animal models of ischemia/reperfusion and sepsis have documented beneficial effects on kidney function [179–182].

Clinical studies

A large prospective randomized controlled trial in 1,548 surgical ICU patients compared tight blood glucose control with insulin (blood glucose 80–110 mg/dL) versus standard care (insulin therapy when blood glucose >200 mg/dL resulting in 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. Additionally, tight glucose control also reduced by 27% the number of patients with peak plasma creatinine >2.5 mg/dL [183]. A similar study was undertaken in the medical ICU of the same hospital where tight blood glucose control again improved survival of prolonged ICU stay but had no effect on the need for RRT. However, there was a 34% reduction in newly acquired renal injury, defined as a doubling of serum creatinine

compared with the admission level [184]. A combined analysis of the two clinical trials, using modified Rifle criteria, showed a more pronounced renal protection when normoglycemia was achieved. The absence of a reduction in the need for RRT in medical patients could be explained by the higher illness severity with more renal dysfunction on admission, precluding an impact of this mainly protective intervention [185]. Two large sequential cohort studies, one in a medical-surgical ICU [186] and the other in the setting of cardiac surgery [187], also revealed a significant reduction in observed renal dysfunction after the implementation of tight glycemic control. Finally, a recent meta-analysis indicated that survival benefit by applying tight glycemic control, if any, may be restricted only to patients in surgical ICUs [188].

More recent randomized trials in septic [65] and general [189, 190] ICU patients and a meta-analysis [191] do not confirm the renoprotective effect of intensive insulin therapy as evaluated by the need for RRT only.

A major obstacle to the broad implementation of tight glycemic control is the increased risk of hypoglycemia. If the clinician decides to adopt tight glycemic control then steps should be taken to ensure that fluctuations in glucose levels are minimized and standardized and that reliable tools to measure blood glucose are employed [192]. An important concern is the fact that the NICE-Sugar trial found a higher mortality in patients treated with tight glycemic control compared with an intermediate level, which was found independent from hypoglycemia [190]. The clinician should, however, be aware of important differences between the Leuven and the NICE-Sugar trial [192] (ESM Table S8).

The use of IGF-1 has not been exposed to as much scrutiny. A multicenter RCT in 72 patients with AKI failed to show an effect of IGF-1 on renal recovery [193]. A small RCT of IGF-1 administered postoperatively in 54 patients undergoing vascular surgery versus placebo did reveal a lower proportion of patients developing renal dysfunction (fall in GFR compared with baseline), but no difference in need for dialysis or creatinine at discharge was observed [194].

The role of thyroxine has been examined in one RCT in 59 patients with AKI. No effect of thyroxine on any measure of AKI severity compared with placebo was found [195].

With regard to the use of corticosteroids for renal protection one small RCT ($n = 20$) has been performed on patients undergoing on-pump cardiothoracic surgery. This failed to demonstrate any effect of dexamethasone on the transient renal impairment observed in the postoperative period [196].

Treatment with APC reduces mortality of patients with severe sepsis [197]. A post hoc analysis of secondary endpoints of this trial, however, failed to show an effect on the resolution of renal failure (measured with the SOFA score criteria) in patients with renal dysfunction at baseline. In patients with normal renal function at baseline there was also no effect on the development of renal impairment [198].

No RCT has evaluated the effect of erythropoietin in AKI. A RCT trial on EPO in critically ill patients showed no difference in the incidence of AKI (mentioned as an adverse event, not as an outcome parameter) [199]. A retrospective cohort study in 187 critically ill patients requiring RRT used a propensity-adjusted analysis and found an improvement in renal recovery in patients administered EPO [198].

Metabolic interventions

Recommendations

1. We **suggest** that all patients at risk of AKI have adequate nutritional support, preferably through the enteral route (grade 2C).
2. We **suggest** that *N*-acetylcysteine is not used as prophylaxis against contrast induced nephropathy or other forms AKI in critically ill patients because of conflicting results, possible adverse reactions, and better alternatives (grade 2B).
3. We **recommend** against the routine use of selenium to protect against renal injury (grade 1B).

Rationale

Metabolic factors are crucial for maintaining cellular integrity and organ function, and nutrition is a basic requirement in the care of any critically ill patients. Starvation accelerates protein breakdown and impairs protein synthesis in the kidney, whereas refeeding might exert the opposite effects and promote renal regeneration. For example, in animal experiments increased protein intake has been shown to reduce tubular injury [200, 201]. Arginine (possibly by producing nitric oxide) helps to preserve renal perfusion and tubular function in both nephrotoxic and ischemic models of AKI. However, amino acids infused before or during ischemia may also enhance tubular damage and accelerate loss of renal function [202]. In part, this "amino acid paradox" is related to the increase in metabolic work for transport processes which may aggravate ischemic injury. However, amino acids per se do not exert intrinsic nephrotoxic effects.

One aspect of nutrition is the adequate supply of nutritional cofactors and antioxidant. The role of reactive oxygen species (ROS) under both normal and pathological conditions has undergone much scrutiny with the NAD(P)H oxidase system believed to be pivotal in their formation and instrumental in the development of certain pathophysiological conditions in the kidney [203–206].

Under certain specific circumstances a role for antioxidant supplementation may be proposed, with potential candidates being the modified form of cysteine, *N*-acetylcysteine (NAC), the antioxidant vitamins [vitamin E (α-tocopherol) and vitamin C (ascorbic acid)], as well as selenium and other novel antioxidants.

Clinical studies

Protein(s) and amino acids, including glutamine, augment renal perfusion and improve renal function, a fact which was termed "renal reserve capacity" [207]. However, this potential beneficial effect has received little attention in terms of prevention and therapy of AKI to date. Intravenous amino acids appear to improve renal plasma flow and glomerular filtration rate in cirrhotic patients with functional renal failure [208]. One study has reported on a positive effect of enteral versus parenteral nutrition on the resolution of AKI [209].

Most studies on antioxidants have centered on NAC, which besides being an antioxidant, also has a vasodilatory effect [210]. NAC undergoes rapid first-pass metabolism through deacylation and as a result its bioavailability is low even following IV administration. There is no evidence that administration of NAC increases glutathione concentrations in the kidney [211, 212]. NAC has mainly been studied in the setting of contrast nephropathy following the initial publication by Tepel et al. [213] which provided the catalyst for the subsequent proliferation of similar studies [127, 213–222]. This subject continues to generate much research and has led to several meta-analysis [152, 223–228] (ESM Table S9). Most report a risk reduction, although study heterogeneity and positive reporting bias somewhat hinders definitive recommendations [229]. However, studies demonstrating a positive effect have a higher incidence of CIN in the control arms, reflecting differences in risk profile, the route of NAC administration, the dose, the timing (with earlier dosing perhaps being more efficacious), and the total contrast load given. Importantly, some investigators suggest that the reduction in serum creatinine with NAC may be a direct effect of the drug on the creatinine measurement and does not reflect a decrease of GFR, although subsequent work has not replicated these findings when serum creatinine is measured via the Jaffe method [230, 231]. An issue of concern is also the fact that the endpoint used in all the studies is a change in creatinine and not clinically relevant endpoints such as a need for RRT, length of stay or death. This is corroborated by a recent study where contrast-induced AKI was not independently associated with death and had no effect on other clinical events [6, 219]. In patients stratified as high or low risk based on GFR, NAC conferred some benefit when combined with hydration, with multivariate analysis confirming age, volume of contrast, diabetes, and peripheral vascular disease as significant factors for CIN development [232]. However, no benefit was observed in studies using NAC in vascular patients [233, 234] nor in diabetic patients when compared with hydration alone [235]. Several recent studies have employed the use of NAC with other agents such as bicarbonate [236, 237], hydration, and theophylline, with mixed results [70, 151, 237–240].

Several RCTs examining the role of NAC to prevent renal dysfunction in other high-risk groups did not demonstrate a beneficial effect of NAC regarding renal dysfunction or need for renal support [241–245] (ESM Table S9), although one study in 177 patients found a mortality benefit for the patients treated with NAC [246]. It must be considered, though, that especially IV NAC may be harmful, leading to allergic reactions [247] or decreased cardiac output or survival in patients with septic shock [248, 249].

A recent single-center trial showed a protective effect of oral ascorbic acid on the development of contrast nephropathy [250]. Here too, the rate of nephropathy in the control group was high and no patients required renal support. Two further studies investigating protection against contrast nephropathy could not prove protective effects of ascorbic acid [72, 251].

There have been several studies on antioxidant supplementation in the ICU, although few large studies have been conducted. The use of an antioxidant cocktail in patients undergoing elective aortic aneurysm repair resulted in an increased creatinine clearance on the second postoperative day but the incidence of renal failure was very low [252].

A a small RCT in 42 patients showed that selenium supplementation decreased the requirement for RRT from 43% to 14% [253]. These findings, however, could not be reproduced in a larger RCT using selenium in 249 patients with sepsis (SIC study) [254, 255]. More recent studies in the critically ill demonstrated that, although selenium supplementation increased both selenium and glutathione peroxidase levels, there was no effect on the requirement for RRT [256].

Extracorporeal therapies

Recommendations

1. We **suggest** periprocedural continuous veno-venous hemofiltration (CVVH) in an ICU environment to limit contrast nephropathy after coronary interventions in high-risk patients with advanced chronic renal insufficiency (grade 2C).

Rationale

Extracorporeal therapies may protect the kidney by removal of substance(s) such as contrast, particularly in patients with chronic renal insufficiency, because of the higher contrast load delivered to the remaining nephrons. The relative amount of contrast removal by hemofiltration depends on the pore size of the filter [257], on hemofiltration dose, and on residual renal function. Control of homeostasis or maintenance of fluid balance may be equally important.

Clinical studies

Several studies have employed renal replacement techniques in an attempt to limit contrast nephropathy. Amongst those, three studies utilized periprocedural hemodialysis, with variable benefit [258–261]. Prophylactic CVVH was evaluated in a total of 114 patients at high risk of contrast nephropathy undergoing coronary intervention. The intervention group had a significantly reduced mortality as well as a reduced need for continued renal support, particularly in those with baseline creatinine >300 μmol/l [262]. The same author performed a second RCT in 92 patients, which demonstrated that only combined pre- and postprocedural CVVH, and not postprocedural CVVH alone, had any renoprotective effect [263]. It should be emphasized that the patients receiving CRRT were treated in ICU and those receiving hydration alone were not, which raises the question of whether the hemofiltration procedure itself or the preprocedural optimization in the ICU environment led to a better outcome. Other mechanisms such as pre- and periprocedural hydration during CVVH, correction of acidosis or control of fluid balance might be relevant [264, 265].

Renal replacement techniques have also been used to ameliorate myoglobin-induced tubular damage in rhabdomyolysis or to remove oxalate following ethylene glycol ingestion. Finally, prophylactic use of extracorporeal treatments in oncology patients at high risk of tumor lysis syndrome has been reported. This available literature is limited to case reports and small case series and no recommendation can be drawn. However, it should be emphasized that fomepizole should be used as a first-line treatment before attempting extracorporeal therapy in cases of ethylene glycol intoxication as well as rasburicase following adequate volume expansion in order to prevent tumor lysis syndrome before consideration of extracorporeal therapy. Similarly, the use of extracorporeal techniques to remove myoglobin will require membranes with a high cutoff [266], possibly used in series for a minimal duration of 6 h, which is not readily available [267–273]. Four studies have evaluated leukodepletion during cardiopulmonary bypass [274–277], with three suggesting a beneficial effect on renal function [274–276].

Conclusions and summary

One of the major problems with any review discussing AKI is the fact that definitions used in many publications vary largely. As a consequence comparing studies is fraught with difficulties and calls for uniformly applicable indicators of severity of renal dysfunction, such as duration and degree of oliguria as well as dependence on renal replacement techniques. Fortunately, initiatives in this direction have recently been taken and should aid further study [5, 278].

In order to prevent AKI, prompt resuscitation of the circulation with fluids, inotropes, vasoconstrictors and/or vasodilators is the primary aim and is recommended. Volume expansion is recommended for the prevention of AKI in states of true and suspected hypovolemia, but uncontrolled volume expansion and the use of high-molecular-weight HES preparations and dextrans should be avoided. Following volume resuscitation hypotensive patients should be given a vasoconstrictor which should be titrated individually, with a mean target blood pressure of 60–65 mmHg being adequate in most individuals. Vasodilators are recommended if optimization of cardiac output or reduction in hypertension is required, and some dilators may be considered to prevent deterioration of renal function under strict hemodynamic control. Together with these measures a review of all medications, with the cessation of those known to be nephrotoxic (e.g., amphotericin B, aminoglycosides), is mandatory.

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