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A European Renal Best Practice (ERBP) Position Statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury†

Part 1: Definitions, Conservative Management and Contrast-induced Nephropathy

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Introduction

The broad clinical syndrome of acute kidney injury (AKI) encompasses various aetiologies, including specific kidney diseases (e.g. acute interstitial nephritis), non-specific conditions (e.g. renal ischaemia) as well as extrarenal pathology (e.g. post-renal obstruction). AKI is a serious condition that affects kidney structure and function acutely, but also in the long term. Recent epidemiological evidence supports the notion that even mild, reversible AKI conveys the risk of persistent tissue damage, and severe AKI can be accompanied by an irreversible decline of kidney function and progression to end-stage kidney failure.[1–3]

The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI[4] were designed to systematically compile information on this topic by experts in the field.

These guidelines are based on the systematic review of relevant trials published before February 2011. Nevertheless, for many sections of the guidelines, appropriate supporting evidence is lacking in the literature. As a consequence, variations in practice will inevitably occur when clinicians take into account the needs of individual patients, available resources and limitations unique to a region, an institution or type of practice. Therefore, in line with its philosophy,[5] the European Renal Best Practice (ERBP) wanted to issue a position statement on these guidelines.

A working group was established to produce guidance from the European nephrology perspective, based on the compiled evidence as presented, with an update of the literature up to March 2012, following the methodology as explained in the ERBP instructions to authors.[6] The present document will deal with the diagnosis and prevention of AKI, and contrast-induced nephropathy (CIN) (Sections 1–4 of the KDIGO document), and other chapters will be discussed in a separate position statement.

As a general rule, we will only mention those guideline statements of the KDIGO document that we have amended, even when the change is small. If a KDIGO recommendation is not repeated, it can be considered as endorsed by ERBP as is, unless specifically stated otherwise.

†This document has been produced according to the instructions for authors of ERBP (see www.european-renal-best-practice.org).

1: AKI Definition

1.1: Definition and Classification of AKI

1.1.1 We recommend using a uniform definition of AKI, based on urinary output and on changes in serum creatinine (SCr) level. It is important that both criteria are taken into account. (1C)

1.1.2 We recommend diagnosing and indicating the severity of AKI according to the criteria in the table below: (ungraded statement)

The ERBP workgroup stresses that this classification should be considered as a severity scoring rather than a nosological definition

1.1.2a We recommend using the first documented serum creatinine value of the episode as 'baseline', rather than historical creatinines or a calculated value based on a presumed glomerular filtration rate (GFR) of 75 mL/min. (1C)

1.1.2b We suggest using 'shift-based' calculation of the urinary output criteria, especially in patients without a bladder catheter (1C). We recommend to use the ideal weight rather than the true weight in calculating the diuresis in mL/min/kg. (Ungraded statement)

1.1.3 The cause of AKI should be determined whenever possible. As a minimal work-up, the presence of hypovolaemia, post-renal causes, low cardiac output, use of nephrotoxic agents, acute glomerulonephritis and renal micro-angiopathy as underlying contributors to AKI should be evaluated. (Ungraded statement)

Rationale

In the past, a myriad of definitions for acute renal failure and AKI existed in parallel, making comparison of results difficult. In the KDIGO Clinical Practice Guidelines for AKI, definition and staging of AKI is based on a combination of the Risk, Injury, Failure; Loss, End-Stage Renal Disease (RIFLE)[7] and Acute Kidney Injury Network (AKIN) criteria.[8] Both criteria rely on GFR, and its proxy serum creatinine, and urinary output as the most useful overall indices of acute changes of kidney function. Changes in serum creatinine concentration and/or urine output are used as surrogates for acute changes in kidney function. The recommended diagnostic criteria establish a solid ground for standardized AKI assessment and classification in everyday clinical practice as well as in research conditions.[9, 10] As such, ERBP considers them as a good starting point towards a more standardized approach to AKI definition and particularly for the assessment of the predictive power of AKI with respect to overall and renal outcome (staging of severity).[11] However, ERBP wants to update and fine-tune the classification by specifically underscoring and more extensively clarifying (i) the need to use the first available (admission) serum creatinine in that episode as baseline creatinine; and (ii) draw attention to the fact that urinary volume should be expressed using ideal body weight rather than real body weight when calculating the urinary output in mL/min/kg. ERBP also felt that it was necessary to explicitly state that both criteria should be applied to classify patients. Indeed, after publication of the RIFLE criteria, it became rapidly apparent that different interpretations were still given to 'baseline creatinine', and that the urinary output criterion was either omitted, or calculated on 24-h urine output.[12, 13] For baseline creatinine, some authors suggested using an estimation of serum creatinine, by backward calculation from a presumed 'standard GFR' of 75 mL/min/1.73 m²; others suggested using the last known value. This concept of a 'universal baseline' clashes with the current epidemiology of AKI, where an important subpopulation do not start from 'normal renal function', but do already have underlying CKD.[14] Siew *et al.* [15] demonstrated that the use of the value at admission in the episode under consideration was best associated with risk. Also in the AKIN criteria, the intention is to use the evolution of serum creatinine relative to the first observed value in that episode.[8] It was demonstrated that using admission creatinine rather than estimated creatinine from a presumed GFR of 75 mL/min improved the prediction of need for renal replacement therapy and mortality,[16] and decreased misclassification.[17, 18] ERBP wants to stress that the use of estimated GFR (eGFR), using whatever formula, is obsolete in patients with AKI, as all these formulae presume that kidney function is stable, and markers of GFR are in steady state, which is of course contradictory with the fact that patients have AKI.

Although diuresis is mentioned in both RIFLE and AKIN, little attention was initially given to it, and many studies on the accuracy of RIFLE did not take into account diuresis. Recent studies point out that diuresis might be a more sensitive marker of AKI than serum creatinine.[19] More importantly, Macedo *et al.* [20] demonstrated that the evaluation of diuresis in 6-h blocks is as accurate as hourly observation. This addresses the argument that diuresis is difficult to measure outside the intensive care unit (ICU): It should be possible, even in general wards, to organize monitoring of diuresis in 6- to 8-h intervals, even in patients without a bladder catheter. In view of the perils and co-morbidities associated with bladder catheterization, ERBP recommends to use 6- to 8-h

observation blocks of urinary output, in patients with spontaneous miction, rather than performing a bladder catheterization just for the sake of hourly urinary output measurements. ERBP recommends that local nephrologists develop and implement strategies to monitor urinary output in hospitalized patients outside the ICU, but are at risk for AKI. Of note, up to 50% of patients with AKI developed this condition at the general ward, not in an ICU.[14] The use of a weight-adjusted urinary volume as the threshold makes some sense, but can lead to overdiagnosis (false-positive diagnosis) of AKI in obese patients or underdiagnosis (false negatives) in cachectic patients. Therefore, ERBP suggests that 'ideal' body weight is considered in these conditions. 'Ideal' should be interpreted as the age, length and gender normalized weight, so, e.g. without oedema. It should also be stressed that urinary output criteria should be evaluated in patients not receiving diuretics.

The additional clinical benefit for differential diagnosis of AKI of newer markers of kidney function (e.g. cystatin C) or kidney injury parameters (e.g. neutrophil gelatinase-associated lipocalin)[21] has so far not been proved and is a matter of debate.[22] ERBP at this stage does not recommend their use for diagnostic purposes in clinical conditions.

As hypovolaemia, post-renal causes and nephrotoxic drugs can result in reversible causes and can be readily diagnosed, these should be excluded as soon as possible. Although their prevalence as a cause of AKI is only limited, a minimal work-up for the presence of underlying rapidly progressive forms of glomerular disease should also be performed, especially in the absence of other potential explanations.

1.2: Risk Assessment

1.2.1 We recommend that patients be stratified for risk of AKI according to their susceptibilities, especially pre-existing proteinuria and CKD, and exposures to nephrotoxic medication or interventions. (1C)

1.2.2 We recommend monitoring patients at increased risk for AKI with measurements of serum creatinine and urine output to detect AKI at an early stage. (Ungraded statement). Frequency and duration of monitoring should be planned based on patient risk and clinical course. (Ungraded statement).

1.2.3 We recommend developing and implementing pathways of care at the broader hospital level, in close collaboration with the other individual specialities, to achieve the above-mentioned targets. (Ungraded statement).

Rationale

Risk for AKI is increased by exposure to factors that cause AKI (e.g. nephrotoxic medication) or the presence of factors that increase susceptibility to AKI [e.g. dehydration, co-morbidities, and also pre-existing proteinuria and chronic kidney disease (CKD)].[23, 24] The interaction between susceptibility and the type and extent of exposure to insults determines the risk of AKI occurrence. Particularly in the hospital setting, the patient's susceptibility should be assessed on a regular basis and some factors modified or even avoided (e.g. administration of potentially nephrotoxic agents). ERBP wants to point out that in patients on dialysis, but with preserved diuresis, it can be of importance to follow-up this parameter after procedures with a risk of deterioration of residual renal function, as unnoticed loss of residual renal function is an important risk factor in this patient group.[25]

As prevention is still the best 'treatment' of AKI, and as many cases of avoidable AKI do not occur in patients in the ICU or on the nephrology ward, but in general wards, ERBP stresses the importance of developing and implementing pathways of care to detect and monitor patients at risk of AKI outside nephrology units and ICUs. These pathways should be developed in collaboration with the different involved specialities, to address the specific needs and risks per particular patient group. Even if patients are only seen after having been exposed to a risk factor, they still should be assessed in order to identify those who are more likely to develop AKI, as well as those who will require closer monitoring and general supportive measures in order to avoid further injury.

1.3. Further Follow-up of AKI

1.3.1 Assess patients 2 months after AKI to evaluate the completeness of resolution, the detection of new onset CKD or worsening of pre-existing CKD. (1C)

Rationale

Observations in recently published epidemiological studies show that in a considerable number of patients who survive the acute clinical condition, CKD develops or worsens.[1–3] Thus, management of patients should extend even beyond the condition of AKI, and should include monitoring for new-onset CKD. Although the follow-up interval after which an assessment should occur is a matter of clinical judgement, we feel that in high-risk in-patients kidney function should be re-assessed not later than 2 months after hospital discharge. Patients should be managed according to appropriate guidelines if CKD is detected.

2: Prevention and Treatment of AKI

2.1: Haemodynamic Monitoring and Support for Prevention and Management of AKI

2.1.1 In the absence of haemorrhagic shock, we recommend using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI. (1B)

2.1.2 We recommend the use of vasopressors to maintain perfusion pressure in volume-resuscitated patients with vasomotor shock with, or at risk for, AKI. (1C)

2.1.3 We suggest using protocol-based management of haemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients. (2C)

Rationale

Patients at increased risk for AKI and particularly those with manifest AKI require careful monitoring of their haemodynamic status, in order to balance the risk of renal hypoperfusion on the one hand and fluid overload on the other. Cardiac output and blood pressure should be kept within optimal limits to ensure the best possible kidney perfusion. However, as recently reported, hazardous fluid overload must be avoided, particularly in anuric patients with AKI.[26] Available therapies to manage hypotension should integrate fluid and vasopressor therapy in protocols with appropriate haemodynamic goals.[27] When volume resuscitation is deemed necessary, there is sufficient evidence[28, 29] to support the recommendation that there is no additional advantage of (more expensive) colloid over crystalloid solutions; therefore ERBP upgraded the strength of this recommendation. However, ERBP wants to stress that this rule does not apply in patients in whom a decrease in the circulating volume is present, e.g. in haemorrhagic shock. In these conditions, the use of colloids can be warranted; iso-osmolar solutions, with low molecular branching coefficients should be preferred. ERBP also wants to point out that the use of large quantities of isotonic saline can potentially lead to metabolic acidosis.

As renal perfusion pressure is more important than renal blood flow per se, and as the action of vasopressors is immediate and directly reversible, ERBP recommends using vasopressor therapy rather than extra fluid in volume-resuscitated patients. Here, norepinephrine[30] has advantages over dopamine, because of fewer side-effects and lower costs, but vasopressin may be used as an alternative. Several meta-analyses have pointed out that dopamine failed to improve outcomes in patients with AKI.[31, 32] Finally, protocol-based goal-directed therapy is advocated in the early hours of sepsis. Such goal-directed therapy includes avoiding hypotension, optimizing oxygen delivery and careful fluid and vasopressor management when indicated.[33] Some clinical studies have highlighted the need to keep mean arterial blood pressure above 65 mmHg in critically ill patients, but the speed of intervention seems to be very important as well.[34]

2.2: General Supportive Management of Patients With AKI, Including Management of Complications

2.2.1 Glycaemic control and nutritional support

2.2.1.1 In critically ill patients, we suggest using insulin therapy to maintain plasma glucose levels between 110 and 180 mg/dL (6.1–8.3 mmol/L) (2C). We recommend implementing this strict glycaemic control only as part of a good functioning glycaemic control protocol, including close monitoring of glycaemia to avoid hypoglycaemia, and the use of flow charts of action. (1A)

2.2.1.2 We suggest not using high-volume continuous renal replacement therapy (CRRT) with the sole aim of administering higher amounts of protein.

2.2.1.3 We suggest providing nutrition via the enteral route as soon as possible in patients with AKI. (1C)

Rationale

There is a well-performed randomized controlled trial (RCT)[35] showing benefit of avoiding hyperglycaemia (>210 mg/dL) in the critically ill. However, this was a single-centre trial, and in a larger randomized multicentre trial of intensive versus conventional insulin therapy, the NICE-SUGAR trial,[36] a blood glucose target of 81–108 mg/dL resulted in higher mortality than a target of <180 mg/dL, without any benefit in preventing or improving AKI. The same study also confirmed previous findings of increased incidence of hypoglycaemia, and the associated risk of death, when targeting low glycaemia levels. In two recent meta-analyses of trials on intensive versus conventional glycaemic control, pooled relative risk of death with intensive insulin therapy was only slightly lower, whereas relative risk of hypoglycaemia was much higher.[37] Lowering glycaemia could thus potentially be beneficial, but this small benefit is easily offset by the much higher risk of hypoglycaemia.[38] Overall, these data do not support the use of intensive insulin therapy aiming to control plasma glucose at 110 mg/dL or lower in critically ill patients as a general rule. On the other hand, it cannot be denied that insulin therapy for preventing severe hyperglycaemia is beneficial. Based on these considerations, ERBP suggests keeping glycaemia between 110 and 180 mg/dL. We strongly recommend regular control of glycaemia, with appropriate instructions on what action should be undertaken based on the result of a certain glycaemic value, when insulin therapy is initiated.

In epidemiological studies, protein–calorie malnutrition is an important independent predictor of in-hospital mortality in patients with AKI, but very few systematic studies have assessed the impact of nutrition on clinical end points. Recommendations are therefore largely based on expert opinion. There is no evidence to support that giving proteins can invert the catabolic process in patients with AKI. According to ERBP, no meaningful guidance can be provided. As such, the ERBP group does not endorse the KDIGO statements relating to administration of proteins. As there is no proven benefit of administering high quantities of protein to patients with AKI, initiating high-volume CRRT with the sole aim to remove extra uraemic waste products resulting from high protein loading, cannot be recommended.

Several RCT's have demonstrated the beneficial effect of providing enteral versus parenteral nutrition in different conditions as soon as possible in ICU patients.[39, 40] A recent large RCT indicated that early initiation of parenteral nutrition in patients not meeting the recommended caloric intakes by enteral feeding leads to higher mortality rates and longer ICU stay.[41] Although these studies have mostly not reported patients with AKI as a separate subgroup, there is no reason to believe that results would be different in this patient group. As parenteral feeding seems not to improve outcomes in a general ICU population, and as parenteral feeding can lead to accumulation of uraemic waste products and increased fluid loading, and thus ultrafiltration need, and, in AKI patients, it should only be used cautiously.

2.2.3 The use of diuretics in AKI.

2.2.3.1 We recommend diuretics should not be used to prevent AKI. (1B)

2.2.3.2 We suggest not using diuretics to increase urinary volume in established AKI, except for the management of volume overload. (2C)

Rationale

Since fluid retention is one of the major symptoms of impaired kidney function, diuretics are often used for patients with or developing AKI. Mostly, loop diuretics such as furosemide are administered to patients with AKI to convert oliguric to non-oliguric AKI, and to facilitate fluid management. However, some reports have indicated that the use of diuretics is associated with harmful effects maybe because circulating volume is reduced excessively, thereby worsening renal haemodynamics. The use of diuretics can also delay the recognition of AKI and nephrology consultation.[42] In meta-analyses, the use of furosemide was not associated with any significant clinical benefits in the prevention and treatment of AKI in adults, and high doses were associated with an increased risk of ototoxicity.[43, 44] The ERBP work group therefore endorses both recommendations on the use of diuretics in patients with AKI.

2.2.4 Pharmacological interventions.

2.2.4.1 We recommend low-dose dopamine should not be used to prevent or treat AKI. (1A)

2.2.4.2 We do not recommend using fenoldopam to prevent or treat AKI. (1C)

2.2.4.3 We do not recommend using atrial natriuretic peptide (ANP) to prevent (1C) or treat (1B) AKI.

2.2.4.4 We do not recommend using recombinant human (rh)IGF-1 to prevent or treat AKI. (1B)

Rationale

With multiple negative studies, including a randomized, double-blind, placebo-controlled trial of adequate size and power, 'low-dose' (1–3 mg/kg/min) dopamine has been abandoned for the prevention and treatment of AKI.[32] Smaller clinical studies have reported a potentially beneficial effect (prevention of need for RRT) of fenoldopam, a pure dopamine Type-1 receptor agonist, in patients with established AKI after cardiothoracic surgery,[45] but larger trials are lacking. In contrast, results on the use of fenoldopam for the prevention of AKI were not positive. Taken together, no data from adequately powered multicentre trials with clinically significant end points and adequate safety are available to recommend fenoldopam to either prevent or treat AKI. In addition, concerns about a potentially harmful dose-dependent hypotensive action, and about the high cost remain. Also, the beneficial impact of norepinephrine on mortality and AKI is well established[30] in these conditions, and should remain as first-line therapy, also in the function of its low cost. As a consequence, ERBP does not recommend the use of fenoldopam. There are no trials to support the use of ANP, urodilatin and brain natriuretic peptide (BNP—nesiritide), for prevention or treatment of AKI. In view of the paucity of robust data from large intervention trials, and the fact that all substances may induce serious adverse effects such as hypotension and arrhythmias, the ERBP group considers that their use cannot be recommended.

The list of substances tested in the setting of experimental and clinical AKI is long, and among them are recombinant human insulin-like growth factor-1 (IGF-1) and recombinant human erythropoietin. As with many other agents, clinical studies on IGF-1 were disappointing. Under these circumstances, the ERBP feels that their use cannot be recommended until proof of a beneficial effect is provided.

2.2.5 Prevention of aminoglycoside- and amphotericin-related AKI.

2.2.5.1 We suggest not using more than one shot of aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (2A)

2.2.5.2 We recommend that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single-dose daily rather than multiple-dose daily treatment regimens. (1B)

An exception to this recommendation can be patients with endocarditis, where inconsistent evidence on non-inferiority of single versus multiple daily dosing is reported. (1D)

2.2.5.3 We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24h. (1A)

2.2.5.4 We suggest monitoring aminoglycoside drug levels when treatment with single-daily dosing is used for more than 48h. (2C)

2.2.5.5 We suggest using topical or local applications of aminoglycosides (e.g. respiratory aerosols, instilled antibiotic beads), rather than intravenous (i.v.) application, when feasible and suitable. (2B)

2.2.5.6 We recommend that patients receiving whatever formulation of amphotericin B should receive adequate sodium loading and potassium suppletion (1B). We suggest balancing the presumed lower nephrotoxicity of lipid formulations against their higher cost. (2D)

2.2.5.7 We suggest balancing the need for adequate antimycotic treatment against the potential risk of nephrotoxicity in selecting the most suitable antimycotic agent. (Ungraded statement)

Rationale

Aminoglycosides are highly potent, bactericidal antibiotics. They have many favourable attributes, including their remarkable stability, predictable pharmacokinetics, low incidence of immunologically mediated side effects and lack of haematologic or hepatic toxicity. Although nephrotoxicity, and ototoxicity, remain major concerns, these events appear to be due to cumulative exposure, and their occurrence after single shot administration is exceptional. On the other hand, due to their potent bactericidal activity, aminoglycosides can help to reverse sepsis-related haemodynamic instability, and thus risk for AKI. In the light of recent developments with progressive antimicrobial resistance to a number of other classes of agents, aminoglycosides remain useful antibiotics. In this perspective, ERBP does not object to the use of aminoglycosides as a single-shot administration in certain conditions. However, careful dosing and therapeutic drug monitoring should be applied to mitigate the risk of AKI with these antibiotics when more than one dose is administered. We recommend that they should be used for as short a period of time as possible.

There are several approaches to avoid nephrotoxicity of amphotericin B in patients at risk. In the opinion of ERBP, the KDIGO guideline has focused too little attention to sodium loading as a potential nephroprotective strategy. Although there is no hard evidence to support the protective effect of sodium loading, the cost is low, and therefore ERBP recommends that it should be implemented in all patients receiving any formulation of amphotericin B. Numerous studies with lipid formulations of this drug have been published. However, a well-performed review on the topic pointed to the high risk of bias in these studies, making the conclusions rather weak.[46] The ERBP believes that there is insufficient evidence to recommend the use of the lipid formulations of amphotericin B as being clearly superior to the conventional formulation. Another approach to prevent amphotericin B nephrotoxicity is to use alternative agents, such as the azoles (voriconazole, fluconazole, itraconazole and posaconazole) and echinocandins (caspofungin, anidulafungin and micafungin). Although these agents have clearly a better record with regard to nephrotoxicity, there is the potential of hepatotoxicity, and there is uncertainty on the therapeutic equivalence. A Cochrane review[47] pointed to substantial biases in the RCT's dealing with this question. In this setting, ERBP believes that the recommendation as issued by KDIGO is too strong, ambivalent and not supported by the evidence. The ERBP workgroup judged that azoles and echinocandines can be used in low-grade infections, but that their role in life threatening infections is unclear, and that in these conditions, the risk of AKI should not outweigh the risk of death by uncontrolled infection.

3. Contrast-induced Nephropathy

Besides the KDIGO guidelines, many other bodies issued recommendations on the treatment and prevention of CIN. As early as 2007, a series of guidelines on the prevention of CIN in high-risk patients undergoing cardiovascular procedures were released,[48] and in 2011, the European Society of Urogenital Radiology (ESUR) released their new guidelines on CIN.[49]

3.1 Definition, Epidemiology and Prognosis

3.1.1 We recommend that for CIN, the same definition and grading is used as for AKI (see 1.1). (Ungraded statement).

3.1.2 We recommend that before an intervention which encompasses a risk for CIN, a baseline serum creatinine should be determined. (Ungraded statement)

3.1.3 We suggest that in high-risk patients, a repeat serum creatinine is performed 12 and 72h after administration of contrast media. (2D)

3.1.4 We suggest not considering only CIN in individuals who develop changes in kidney function after administration of intravascular contrast media, but also other possible causes of AKI. (Not Graded)

Rationale

The ERBP work group is not aware of any pathophysiological or epidemiological reason why the definition and staging of CIN should be different from the general AKI definition. This definition is slightly different from the ESUR criteria[49] for contrast-induced nephropathy, which requires an increase in SCr by more than 25% or 44 µmol/L in the 3 days following intravascular administration of contrast medium (CM) in the absence of an alternative aetiology. Thus, many patients with an SCr increase ranging from 26.5 to 44 µmol/L following CM administration would be considered as presenting Stage 1 AKI but not as CI nephropathy. However, for the sake of clarity and uniformity, ERBP recommends to use the general AKI criteria. Remarkably, studies have also pointed out that in many hospitalized patients not receiving contrast, an increase in serum creatinine was observed.[50] As such, in patients who did receive contrast, one should be cautious to attribute AKI to the contrast, and other underlying causes for AKI should be explored.

The moment when the repeat serum creatinine should be measured is a matter of debate. According to ESUR, it should be done in the 3 days following intravascular administration of CM. Some studies suggest that the peak of SCr could even occur later, especially in patients with diabetes and pre-existing CKD[51–56] which really underlines the need for an extended period of renal function survey. On the other hand, the percentage increase in serum creatinine from baseline after 12h showed a good prediction for later development of renal impairment.[57]

The reliability of other renal function markers such as cystatin C should be further evaluated.

On the other hand, the importance of urinary output for diagnosing CIN should be emphasized.

3.2.1 We recommend balancing the risk for CIN against the benefit of administering contrast. (Not Graded)

3.2.2 We recommend considering alternative imaging methods not requiring contrast administration in patients at increased risk for CIN, so long as these yield the same diagnostic accuracy. (Not Graded)

Rationale

Although these recommendations seem trivial, it is important to balance the potential risk of CIN against the potential gain of administering contrast in the clinical decision process.

Risk for CIN increases with decreasing pre-existing GFR. A CIN Consensus Working Panel[58] agreed that CIN risk becomes clinically significant when the baseline SCr concentration is ≥1.3 mg/dL (≥115 mmol/L) in men and ≥1.0 mg/dL (≥88.4 mmol/L) in women, mostly equivalent to an eGFR <60 mL/min/1.73 m^2. In light of more recent work,[50] the ERBP work group agrees with KDIGO that this threshold could be lowered to 45 mL/min/1.73 m^2.

The risk of CIN also increased in the presence of diabetes, and dehydration. The risk may be lower when simple i.v. contrast is administered for imaging versus when contrast is used during an invasive intra-arterial procedure, where the risk of cholesterol embolization should also be taken into account.[59] It is unclear whether simple

intra-arterial injection, e.g. digital subtraction angiography has a different risk from i.v..[60, 61]

The risk increases with the volume of contrast applied. There are no data available to know if the effect of repeated contrast administration is simply a consequence of the cumulative dosage of iodine, or whether repeated administrations are disproportionately more toxic than the administration of a certain volume of contrast in one shot.

Another risk factor is the use of concurrent nephrotoxic medication: non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, high doses of loop diuretics and antiviral drugs like acyclovir and foscarnet, in particular. A special mention should be made on metformine, as accumulation of this drug in CIN can lead to dangerous situations. The ERBP group wants to point out that several drugs have a prolonged nephrotoxic action as a consequence of a long-lasting cellular accumulation in the kidney. In order to minimize the risk of kidney damage, these drugs would have to be stopped for days or even weeks, and not only hours, before contrast administration. The rationale for stopping loop diuretics is mainly based on their detrimental effect if used as pharmacological prevention against CIN.[62] Not only must loop diuretics be discontinued during and after contrast administration, but they should be stopped for as long as possible before the procedure in order to reduce the possibility of volume depletion. From this point of view, it is surprising to note that the possible detrimental effect of thiazide diuretics, which have a much longer action period, is almost never mentioned. It should be stressed that dehydration or any degree of volume depletion make medullary renal perfusion closely dependent of vasoactive hormones, and extremely sensitive to microvascular effects of intravascular contrast administration.[63] Apart from diuretics, clinical circumstances such as gastro-intestinal fluid losses may induce dehydration, and if possible it is wise to delay contrast administration until volume status has been corrected.

To date, there is very little evidence on the detrimental effects of angiotensin-converting enzyme-inhibitor (ACE-I) concerning the renal risk of contrast administration. A randomized study showed a decreased incidence of CIN following the administration of captopril in diabetic patients undergoing coronary angiography,[64] and more recently, it was observed that a captopril treatment stopped 36h before CM administration was neither associated with nor increased the risk of CIN in hydrated patients.[65] However, the risk associated with long-acting ACE-I and ARB is poorly defined and should be assessed through specific studies.

Pharmacological Prevention Strategies of CIN

3.4.1 We recommend volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no volume expansion, in patients at increased risk for CIN. (1A)

3.4.2 We suggest using the oral route for hydration, on the premise that adequate intake of fluid and salt are assured. (2C)

We suggest that, when oral intake of fluid and salt is deemed cumbersome in patients at increased risk of CIN, hydration should be performed by intravenous route. (2C)

3.4.3 We suggest using oral N-acetyl cysteine (NAC) only in patients who receive appropriate fluid and salt loading (2D). We recommend not using oral NAC as the only method for prevention of CIN. (1D)

3.4.4 We do not suggest using theophylline to prevent CIN. (2C)

3.4.5 We do not recommend using fenoldopam to prevent CIN. (1B)

Rationale

There is no doubt that before contrast media administration, adequate salt and fluid should be provided to prevent CIN

The ERBP work group amended the statement on oral fluid loading by the KDIGO work group, as this was

based on two small and relatively old studies, in which oral fluid intake did not confer the same degree of protection against CIN than i.v. fluid administration.[66, 67] However, a recent observational study showed a significant inverse correlation between the amount of oral fluid intake and the percentage changes in SCr as well as the absolute changes in eGFR in patients undergoing a coronary computed tomography angiography,[68] and a prospective randomized trial comparing i.v. fluids with oral hydration with or without sodium bicarbonate found no differences in the incidence of CIN in patients with mild CKD.[69] It should be noted that the main difference between oral and i.v. fluid administration concerns not only the volume but the sodium content of the fluids as well.[70] In ambulatory patients, the i.v. route leads to a substantial increase in costs, and a risk for destruction of future vascular access. The ERBP work group accordingly does not recommend hospitalizing low-risk patients just for hydration. Most of the ambulatory patients have a relatively low risk for CIN, and in these patients, oral hydration should be recommended. When i.v. access is in place anyway, e.g. in hospitalized patients, the i.v. route can be used.

NAC has a number of beneficial properties, including anti-oxidant functions and mediation of renal vasodilation, making it a suitable candidate to help prevent CIN. However, NAC has been the subject of a series of comprehensive reviews, and overall there appears to be insufficient evidence to support the universal use of NAC to prevent CIN despite its ease of administration.[63] It should be noted that in most trials reporting a benefit, NAC administration was associated with i.v. hydration using bicarbonate. Studies of NAC with bicarbonate administration have found a moderate benefit for this combination, compared with the combination of NAC–saline, and it is unclear in how far the benefit can be attributed to NAC per se. To date, 7 out of the 11 meta-analyses that have been published on this subject found a net benefit for NAC in the prevention of CIN.[71] NAC, however, has been reported to decrease SCr levels in normal volunteers with normal kidney function. This reduction in SCr was not accompanied by a change in serum cystatin C levels, suggesting an effect independent of a change in GFR, such as an increase in tubular secretion of creatinine or a decrease in creatinine production.[72] In conclusion, in view of its low costs and the high likelihood of absence of harm, there is no objection against oral NAC administration, but this should never replace adequate fluid loading.

Effects of Haemodialysis or Haemofiltration

4.5.1: We do not recommend using prophylactic intermittent haemodialysis (IHD) or haemofiltration (HF) for the purpose of prevention of CIN only. (1C)

Rationale

The evidence collected by KDIGO demonstrates that IHD to prevent CIN in well pre-hydrated patients at risk is not effective, and that there is even a trend to more harm (more CIN, and more need for RRT).[73–75] High-volume HF in this setting has been reported to be beneficial.[76, 77] The protocol used in these studies included HF at ICU, and with high volumes of bicarbonate fluid. It seems likely that under these conditions, the beneficial effects observed were due to volume expansion and loading with bicarbonate rather than to the removal of contrast media by the HF. In view of the high costs and logistical problems, the evidence seems too weak to recommend prophylactic HF at this moment.

Sidebar

Stage 1: one of the following:

- Serum creatinine increased 1.5–1.9 times baseline
- Serum creatinine increase >0.3mg/dl (26.5 µmol/l)
- Urinary ouotput < 0.5ml/kg/h during a 6 hour block

Stage 2: one of the following

- Serum creatinine increase 2.0–2.9 times baseline
- Urinary output <0.5ml/kg/h during two 6 hour blocks

Stage 3: one of the following:

- Serum creatinine increase >3 times baseline
- Serum creatinine increases to >4.0mg/dl (353 µmol/l)
- Initiation of renal replacement therapy
- Urinary output <0.3ml/kg/h during more than 24 hours
- Anuria for more than 12 hours

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