Section 4. CONTRAST INDUCED ACUTE KIDNEY INJURY

Authors: Martin Gallagher, Vincent D'Intini

GUIDELINES

a. We recommend using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media, in patients at increased risk of CI-AKI. (1B)

Since iohexol use as an intra-arterial injection in patients with pre-existing renal impairment is associated with an increase in CI-AKI risk when compared to iodixanol, we suggest avoiding iohexol use in this high risk setting. (1B)

b. We recommend IV volume expansion with isotonic saline or sodium bicarbonate, rather than no IV volume expansion, in patients at increased risk for CI-AKI. (1A)

We suggest that isotonic sodium bicarbonate for IV volume expansion is at least equivalent to isotonic sodium chloride in prevention of CI-AKI. (2A)

c. We suggest oral route of hydration may be beneficial compared to fasting state in reducing the risk of CI-AKI in patients at increased risk for CI-AKI. (2C)

d. We suggest that the use of oral NAC, in addition to IV isotonic crystalloids, in patients at increased risk for CI-AKI is not of proven benefit. (2A)

e. We recommend not using prophylactic intermittent haemodialysis (IHD) or hemofiltration (HF) for contrast media removal in patients at increased risk for CI-AKI. (1C)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

- Define and stage AKI after administration of intravascular contrast media as per currently adapted guidelines [CARI KDIGO AKI guideline adaptation, Section 1, Definition and Classification of AKI] (Ungraded)

- Assess the risk for CI-AKI using tools such as medical history, physical examination and in higher risk groups, laboratory investigations in all patients who are considered for a procedure that requires intravascular administration of iodinated contrast medium (Ungraded)
The optimal imaging modality for the likely diagnoses should always be considered. In patients at increased risk for CI-AKI, the balance of all risks and benefits of the imaging modality should be evaluated. (Ungraded)

- Use the lowest possible dose of contrast medium in patients at risk for CI-AKI (Ungraded)

IMPLEMENTATION AND AUDIT

Individual units should consider an audit of the rates of AKI associated with the use of iodinated contrast agents; in particular when CI-AKI is severe enough to require renal replacement therapy.

BACKGROUND

Contrast-media is commonly used in a variety of diagnostic scans, including: X-rays, CT scans, MRI and ultrasounds, a known complication includes contrast-induced acute kidney injury (CI-AKI) [1]; which is reported to be frequent in both ambulatory and hospitalised patients. One study indicating that 1 in 6 ICU patients undergoing contrast-media examination developed CI-AKI [2]. The high use of contrast-media radiography and its association with CI-AKI causes adverse outcomes for patients: increased risks of morbidity and mortality, longer hospital stay and potential need for renal replacement therapy [2, 3].

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 21 in the Appendix of the KDIGO guideline) (Kidney International Supplements 2 (2012); 2: 102-113). Additional key papers have been identified by the authors that were published after the KHA-CARI update search.

Databases searched: Medline, Central, Cochrane database of systematic reviews

Date of searches: June 2012

ADEQUACY OF KDIGO SEARCH STRATEGY

The search strategy and evidence provided by KDIGO was comprehensive and included some important randomised controlled trials (RCTs). A number of systematic reviews and RCTs have subsequently been identified in the updated search by KHA-CARI and included in this update.
APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO recommendations and suggestions are considered appropriate for use in Australia and New Zealand. There have been subtle changes made based on more recent evidence and interpretation of reviewed evidence. This has also affected grading of some of the recommendations.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI, as part of the adaptation process.

a. We recommend using iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media, in patients at increased risk of CI-AKI. (1B)
Since iohexol use as an intra-arterial injection in patients with pre-existing renal impairment is associated with an increase in CI-AKI risk when compared to iodixanol, we suggest avoiding iohexol use in this high risk setting. (1B)

Guideline 4a is unaltered in text and grading from the KDIGO document (guideline 4.3.2). Whilst there were 5 papers relevant to this guideline identified in the KHA-CARI updated literature search, only one of these impacted upon the recommendations. This paper [4], published in 2009, was a meta-analysis of randomised trials comparing iso-osmolar iodixanol with non-ionic low osmolar contrast media and was discussed in the KDIGO document but not included as part of the guideline statement. The main finding of this meta-analysis was that the risk of nephrotoxicity with iodixanol was not different to that with all low osmolar contrast media (RR 0.68, 95% CI 0.46 – 1.01, p = 0.06). However, in patients with pre-existing renal impairment and receiving intra-arterial contrast, the risk of CI-AKI was lower using iodixanol compared to one low osmolar contrast agent, iohexol (RR 0.38, 95% CI 0.21 – 0.68, p <0.01). In view of the quality of this meta-analysis of randomised studies and the effect size seen, we took the view that his finding justified a separate guideline statement.

b. We recommend IV volume expansion with isotonic saline or isotonic sodium bicarbonate, rather than no IV volume expansion in patients at increased risk for CI-AKI. (1A)
We suggest that isotonic sodium bicarbonate for IV volume expansion is at least equivalent to isotonic sodium chloride in prevention of CI-AKI. (2A)

Guideline 4b is unaltered in grading from the KDIGO document (guideline 4.4.1) with only minor alterations in the text to enhance readability. There were a number of papers germane to this guideline identified in the KHA-CARI updated literature search but there were no studies of scale, quality or...
outcome that were sufficient to change the existing guideline recommendations. The KDIGO Guideline did not express an opinion upon the relative merits of intravenous saline and bicarbonate, devoting a paragraph to explaining the rationale for this decision. Numerous meta-analyses have addressed this issue, with some suggesting a benefit from pre-procedure hydration with bicarbonate. Meier et al 2009 [5] found a decrease in CI-AKI with bicarbonate usage compared to saline with a noteworthy effect size (OR 0.52, 95% CI 0.34 – 0.80, p = 0.003). A subsequent meta-analysis from Zoungas et al [6], suggested that this effect was likely to have been overestimated by the presence of publication bias and poor study quality.

In view of the fact that his question has generated many publications, including meta-analyses, and is an oft-posed question by clinicians, we felt that some guidance should be provided upon the current state of knowledge. We also highlight the advice in the KDIGO guideline regarding the fact that the administration of pre-hydration using bicarbonate solutions is more complex than saline, and therefore is likely to carry some additional risks that may not have been well measured in the clinical trials to date.

c. We suggest oral route of hydration may be beneficial compared to fasting state in reducing the risk of CI-AKI in patients at increased risk for CI-AKI. (2C)

We have altered this statement from the KDIGO guideline (guideline 4.4.2) which states ‘We recommend not using oral fluids alone in patients at increased risk of CI-AKI’. KDIGO qualified this by stating that there was not enough evidence available to adequately compare intravenous versus oral hydration. There are now six small RCTs with 513 patients comparing oral versus intravenous volume expansion that have been summarised in a recently published meta-analysis (published after the date of KHA-CARI guideline literature search [7]). This review did not demonstrate a difference in the rates of CI-AKI between the two modalities of hydration.

The number of patients included in these studies is small, with only 45 CI-AKI events, and there exist significant limitations to the studies. Factors such as heterogeneity in the amount of contrast received, baseline GFR and route of contrast administration weaken this evidence. Distilling this evidence, we have concluded that there is not enough evidence to say that oral hydration is clearly inferior to IV hydration. Given that IV hydration is the recommended therapy for CI-AKI prevention, but that it is not viable (due to cost and time difficulties) for all occasions of contrast exposure, this guideline is a logical extension from the currently available evidence. It does not comment upon the comparison of IV versus oral hydration.
d. We suggest that the use of oral NAC, in addition to IV isotonic crystalloids, in patients at increased risk for CI-AKI is not of proven benefit. (2B)

This guideline statement differs significantly from the KDIGO Guideline, which suggests using NAC, together with IV isotonic crystalloids, in patients at risk of CI-AKI.

The quality of evidence supporting the KDIGO suggestion is assigned the lowest level of D, defined as where “the estimate of effect is very uncertain, and often will be far from the truth”. The question of the utility of NAC in preventing CI-AKI has been bedevilled by numerous meta-analyses based upon many small studies that use varying clinical settings, different end points and are of mixed methodological quality, with publication bias at play in the background. Drawing a robust conclusion in this setting is fraught and, whilst KDIGO chose to support the use of NAC as it is a cheap and low cost treatment, we felt that whilst equipoise exists we should not be suggesting its use.

One additional advance since the KDIGO Guideline’s publication is the publication of the Acetylcysteine for Contrast-induced Nephropathy Trial (ACT) in 2011 [8]. This study is undoubtedly a leap forward in scale and study design in the field, recruiting 2308 patients undergoing an intra-arterial angiographic procedure with at least 1 risk factor for CI-AKI and randomising them to NAC or placebo. They found no difference in the incidence of CI-AKI (using a 25% increase in serum creatinine between 48 and 96 hrs after angiography) between the two groups. We felt that this study supported the alteration of the KDIGO guideline and that the evidence quality was of a moderate level.

e. We recommend not using prophylactic intermittent haemodialysis (IHD) or haemofiltration (HF) for contrast media removal in patients at increased risk for CI-AKI. (1C)

To date extracorporeal blood purification has not been beneficial in patients at increased risk for CI-AKI. There is some evidence to suggest a trend in causing more harm. This intervention is costly and potentially deleterious with no evidence of benefit. Hence the higher grade.

UNGRADED SUGGESTIONS

- Define and stage AKI after administration of intravascular contrast media as per currently adapted guidelines [CARI KDIGO AKI guideline adaptation, Section 1, Definition and Classification of AKI] (Ungraded)

Refer to Section 1 of the CARI KDIGO AKI guideline adaptation.

- Assess the risk for CI-AKI using tools such as medical history, physical examination and in higher risk groups, laboratory investigations in all
patients who are considered for a procedure that requires intravascular administration of iodinated contrast medium (Ungraded)

We have altered the text of this guideline from that in the KDIGO document on the basis of a number of factors, including the paucity of evidence, the primacy in risk assessment given to renal dysfunction and the limited emphasis given to other risk factors.

The evidence base for this guideline is very weak. The major supporting literature cited in the KDIGO guideline comes from a consensus statement [9], a small retrospective audit [10] and two risk assessment algorithm papers [11,12], with an updated search for this adaptation not deriving any additional contributory literature. The risk assessment papers are both derived from the clinical setting of coronary interventions which, although likely represent a high risk patient group and clinical setting, are only a fraction of all procedures that expose patients to the risk of CI-AKI.

The KDIGO guideline statement recommends screening for renal dysfunction in all patients undergoing contrast exposure and, in the absence of suggesting how this might be done, could be interpreted as recommending screening blood tests for all. Such universal use of screening blood tests is not supported by the current literature and would appear unlikely to be feasible until there are significant advances in the cost and accuracy of point-of-care creatinine testing. The guideline gives primacy to this assessment of renal dysfunction by giving particular emphasis to it as a risk factor. The limited literature suggests that CI-AKI has a number of risk factors (including age, diabetes, and presence of cardiac failure, hypotension, anaemia, volume and type of contrast media used) and it would seem that the confluence of multiple risk factors is likely to represent the situation of greatest risk for CI-AKI. The CI-AKI risk prediction algorithms would support such an approach. In addition, many of these risk factors can be assessed using history or physical examination.

The text of the KDIGO guideline mentions the widely held view that intra-arterial contrast administration carries a higher risk of CI-AKI than intra-venous administration. Testing this difference is challenging due to the difficulty in establishing comparative control groups, as the different routes of administration are not readily interchangeable. The literature search for this adaptation did not give rise to any new literature that better informs the relative risks, which have been poorly characterised.

Accordingly, we have altered the text of the guideline in an attempt to remove any un-due emphasis upon renal dysfunction alone as a risk factor, to encourage the use of clinical tools to assess risk and to avoid any impression of the need to resort to laboratory investigations in all those being exposed to intravenous or intra-arterial iodinated radio contrast agents.

- The optimal imaging modality for the likely diagnoses should always be considered. In patients at increased risk for CI-AKI, the balance of all
risks and benefits of the imaging modality should be evaluated. (Ungraded)

This adapted statement is also slightly different from the original KDIGO statement (guideline 4.2.2). The evidence base to shape this guideline is very limited and only non-graded statements are possible. Our changes to the statement were made because the existing KDIGO statement does not countenance the balance of risks and benefits that flow from considering or using alternative imaging modalities. We felt this should be made explicit in the statement.

- Use the lowest possible dose of contrast medium in patients at risk for CI-AKI (Ungraded)

It is important to take into consideration that there exists large variation in the concentration of the commercially available contrast media meaning that recommendations on the actual dose of contrast are not possible.

**WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcome Quality Initiative (2013): [13]**

1. All patients undergoing contrast-enhanced imaging procedures should be evaluated for risk of AKI. Screening can most appropriately be performed using standardized questionnaires. Routine measurement of serum creatinine in patients identified as low risk by questionnaire is not indicated; however, if there is any question regarding risk of kidney disease, serum creatinine level should be obtained prior to contrast administration.

2. The risks and benefits of contrast administration need to be carefully evaluated in patients at high risk of contrast-induced AKI. The risk of contrast-induced AKI should not preclude the performance of needed diagnostic imaging and therapeutic procedures in high-risk patients.

3. Iso-osmolal or selected low-osmolality contrast in the lowest possible dose should be used in high-risk patients.

4. The only intervention that has consistently been demonstrated to decrease the risk of contrast-induced AKI is peri-procedural intravenous volume administration using isotonic crystalloid. Thus, all patients at increased risk of contrast-induced AKI should receive peri-procedural intravenous isotonic crystalloid. The optimal rate of fluid administration remains uncertain, and whether bicarbonate administration is associated with greater benefit at risk reduction than saline remains unresolved.
5. The benefit associated with NAC administration remains uncertain. Given the minimal risk and cost associated with this agent, we do not recommend against its use, although it should not be used in lieu of more effective interventions, particularly peri procedural administration of isotonic crystalloid.

**UK Renal Association (2011): [14]**

3.3 We recommend that patients identified as being at risk of contrast induced-AKI (CI-AKI) should have a careful assessment of volume status and receive pre-procedure volume expansion with 0.9% sodium chloride or isotonic sodium bicarbonate if clinically indicated. (1A)

3.4 We recommend that patients identified as being at risk of developing AKI secondary to rhabdomyolysis should receive intravenous volume expansion with 0.9% sodium chloride and sodium bicarbonate. (1B)

**Canadian Society of Nephrology (2013): [15]**

Use of low-osmolar iodinated contrast media is not recommended in patients at low risk of contrast induced AKI, due to high costs of these agents. Use of iso-osmolar agents are reserved for patients at high risk of contrast-induced AKI.

**European Renal Best Practice Guidelines (2012): [16]**

3.1.1 We recommend that for CIN, the same definition and grading is used as for AKI (see 1.1). (Ungraded statement).
Which differs from the KDIGO guidelines (takes into account both Scr and urine output).

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 72 h 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)

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)
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)

SUGGESTIONS FOR FUTURE RESEARCH

1. Preventative strategies with volume expansion still requires more RCTs for more robust recommendations around issues with fluid type (oral or intravenous), timing (pre and post) and rate.
2. Novel contrast agents with little or no nephrotoxicity would have significant impact on this field mitigating CI-AKI complications and prevention interventions.
3. Novel agents that prevent CI-AKI would be beneficial when fluid and volume issues are a concern.

CONFLICT OF INTEREST

M.P. Gallagher received an honorarium from Amgen and Abbvie; Amgen also sponsor a research fellowship at The George Institute.

V D’Intini received financial support from Servier to attend the DNT Workshop in Alice Springs in March 2013.
REFERENCES


