ABSTRACT

Background. Contrast-induced acute kidney injury (CI-AKI) is a potential complication of radio-contrast investigations. Many organisations have published guidance documents on the prevention of CI-AKI. Our aim is to explore the scope, content, consistency, practicality in clinical practice and reasons for eventual underlying discrepancies of these documents.

Methods. We searched the literature for guidance documents developed to guide prevention of CI-AKI up to 09/2014. Four reviewers appraised guideline quality using the 23-item AGREE-II instrument, which rates reporting of the guidance development process across six domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. Total scores were calculated as standardised averages by domain.

Results. Twenty-four guidance documents were evaluated. The guidance documents were produced by radiologists (N = 7), intensivists (N = 2), nephrologists (N = 6) or multidisciplinary teams (N = 9). One document did not mention the background of the authors. Only guidance documents (N = 15) that were not mere adaptations of existing guidelines were evaluated more in depth, using the AGREE tool. Overall, quality was mixed: only one clinical practice guidance document obtained an average score of >50% for all domains. The evidence was rated in a systematic way in only 11, and only 7 graded the strength of the recommendations. The Kidney Diseases Improving Global Outcomes guideline was the only one recommended without adaptions by all assessors. The guidance documents agreed in recommending pre-hydration as the main preventive measure, but there was difference in recommended total volumes, composition, rate and duration of the infused solutions. There was no consensus on the use of NaHCO₃, with eight recommending it, six considering it and one not. Five guidance documents mentioned oral pre-hydration as a possibility, and none recommended N-acetylcysteine as solitary preventive measure. More recent guideline documents recommend avoiding hypertonic contrast media, but did not recommend preference of iso-osmolar over low-osmolar contrast media. Most guidance documents recognised pre-existing chronic kidney disease, diabetes, age and cardiovascular comorbidity as risk factors.

Conclusions. There seems to be a relative consensus on the need for adequate pre-hydration to avoid CI-AKI, but recommendations to define at-risk populations for whom these measures should be applied and how they should be implemented differ substantially. Based on accumulating evidence, more recent guidelines do not recommend iso-osmolar over low-osmolar contrast media, whereas all recommend avoiding hypertonic agents.

Keywords: AGREE-II, CI-AKI, clinical guidelines, pre-hydration, prevention

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI), formerly called contrast nephropathy, has been defined as a sudden decline in kidney function after the intravascular administration of iodinated contrast media for diagnostic imaging. CI-AKI is a common cause of community- or hospital-acquired AKI, especially in patients with pre-existing risk factors, and this

Original Article

Selecting a strategy for prevention of contrast-induced nephropathy in clinical practice: an evaluation of different clinical practice guidelines using the AGREE tool

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complication is associated with prolonged hospitalization, relevant morbidity, early and late mortality and increased health care costs [1].

Although the definition of CI-AKI varies across studies, the most commonly used definition has been an increase in the serum creatinine concentration (Scr) of at least 0.5 mg/dL (44 µmol/L) and/or of 25% within 3 to 4 days after contrast exposure [2–6].

Over the last decade, an impressive bulk of research has been published on each of these topics, often with conflicting conclusions. For the practising clinician, it is nearly impossible to correctly interpret and follow this literature. Several aspects of the management of CI-AKI are still a matter of debate. Among these, the definition (and thus epidemiology and prevalence) of CI-AKI, risk factors, use of bicarbonate versus sodium chloride-based solutions, oral versus intravenous pre-hydration, use of N-acetylcysteine and the use of iso-osmolar contrast media are the most relevant. In view of its alleged impact on patient outcomes and quality of care and the vast and conflicting literature, it is not surprising that a substantial number of clinical practice guidelines (CPGs) on the prevention, management and prognosis of CI-AKI have been published. For the end-user of these guidelines, it is not directly clear whether these guidelines provide comparable quality and advice and, if not, which of them offers the most appropriate advice to be implemented in clinical practice.

It is critically important to be certain that guideline development is scientifically rigorous and free of inappropriate bias from anyone who might financially benefit from particular guideline recommendations. Quality of the guidelines can be defined as ‘the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice’. To address the issue of variability in guideline quality and to assess the methodological rigour and transparency in which a guideline is developed, instruments such as the ‘Appraisal of Guidelines for REsearch & Evaluation’ (AGREE) have been developed [7]. Meanwhile, a multitude of papers using AGREE to evaluate guidelines on different topics have been published, confirming that there is huge variability in recommended practices between guidelines [8]. For most of the cases, these differences can at least partially be explained by lack of methodological rigour in the development of the guideline. In cases of a clinical topic that involves different specialties, these differences can at least partially be explained by lack of methodological rigour in the development of the guideline.

As CI-AKI is a prevalent and clinical problem and is relevant to many specialties, the present paper, using the AGREE tool, aims at an evaluation of the quality of different available guidance documents and their recommendations on different aspects of CI-AKI.

**METHODS**

We searched the literature by reviewing websites of professional organisations that might have an interest in CI-AKI, including societies of radiology, cardiology, nephrology and intensive care. In addition, we searched Pubmed, combining mesh terms for ‘acute kidney injury’ and ‘contrast’, for published guidance documents from 1/2007 till 9/2014. Only guidance documents published in English and authored by representatives of professional groups were included. The search was not constructed with the intention to be exhaustive; we rather aimed to retrieve guidance documents that would pop up with a simple search strategy; papers that were not more than adaptations of existing guidance were not considered.

Four reviewers independently assessed the methodological quality of the guidance documents, using the Appraisal of Guidelines for Research and Evaluation (AGREE-II) instrument [9]. AGREE-II is an internationally validated, rigorously developed 23-item tool used to evaluate six domains of guideline development: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. The AGREE tool has also been used to assess consensus statements [10–12]. The reviewers rated each item on a Likert scale from 1 (‘strongly disagree’) to 7 (‘strongly agree’). We calculated a total score for each domain by summing up all the scores of the individual items in a domain for each reviewer and then standardizing this total as a percentage of the maximum possible score for that domain, calculated as follows [7]:

\[
\text{Obtained score} - \text{minimum possible score} \times 100\%.
\]

The minimum possible score for each domain equalled the number of questions multiplied by the number of reviewers, multiplied by 1 (strongly disagree). The maximum score for a domain equalled the number of questions multiplied by the number of reviewers, multiplied by 7 (strongly agree). To ensure standardization of each reviewer’s approach, all completed the online training tutorial (http://www.agreetrust.org/) before starting the project.

In a consensus meeting, the reviewers discussed every item for which scores differed by more than one point (e.g. 1 versus 3) on the original seven-point scale. Reviewers in turn explained the rationale for their score and had the opportunity to revise their score when they considered this appropriate. We audio-taped the consensus meeting to reliably record the underlying reasons for changing scores.

**Synthesis of guideline recommendations**

A textual descriptive synthesis to analyse the scope, content and consistency of the included recommendations was conducted. Predefined topics of interest (involved specialties, involvement of nephrologists, clear definition of CI-AKI, timing of CI-AKI, definition of CI-AKI, risk factors, serum creatinine before contrast, preventive regime, oral versus intravenous hydration, use of N-acetylcysteine, use of NaHCO₃, kind of contrast agent and volume of contrast) were cross-tabulated from the guidelines and recommendations and were inserted into an Excel sheet template. For each domain, guideline recommendations were compared to identify similarities and discrepancies.
RESULTS

We evaluated 24 guidance documents [13–36]. These guidance documents were issued by societies of radiologists (n = 7), intensivists (n = 1), nephrologists (n = 6) or multidisciplinary teams (n = 9). For one guidance document, the issuing specialty was unclear. Nephrologists were involved in the production for half of the guidelines (12/24) (Supplementary data, Table S1).

Fifteen of the guidance documents were based on new evaluation of the literature rather than a comment or extension of existing evidence and were evaluated using the AGREE-II instrument. On average, most of the articles obtained low to mediocre scores using this instrument, as demonstrated in Figure 1. Overall score was 44.3 ± 21.6% (median 44%). Only the NICE guideline [16] passed in all of the appraised domains, whereas the Kidney Diseases Improving Global Outcomes (KDIGO) guideline [13] obtained an unsatisfactory result only in the domain of applicability. The scores for the different domains were 43.5 ± 16.7% (general scope and purpose, median 44%), 36 ± 18.2% (stakeholder involvement, median 31%), 39.0 ± 24.3% (methodological rigour of development, median 26%), 53.3 ± 13.8% (clarity of presentation, median 57%), 23.8 ± 13.8% (applicability, median 18%) and 35.8 ± 30.8% (editorial independence, median 25%).

Regarding the overall assessment, the only guidance document of sufficient quality to be recommended for use without modifications by the review team was the KDIGO Clinical Practice Guideline for Acute Kidney Injury [13]. Despite a few shortcomings in the domain of applicability, this guideline was considered the best by the AGREE-II reviewers. All reviewers agreed that the NICE guideline on Acute Kidney Injury [16] also performs well enough to be recommended, provided some minor adaptations are adopted. Both the KDIGO and the NICE guideline cover AKI in general, and not only CI-AKI.

Furthermore, the textual content of all 24 guidance documents was checked and tabulated. Only 15/24 of the guidance documents stated a clear definition for CI-AKI or AKI in general (Supplementary data, Table S1). Most of the authors agreed about the timing of CI-AKI, as occurring between 48 and 72 h after contrast administration.

According to most (21/24) guidance documents, pre-existing chronic kidney disease (CKD) is the most important risk factor for CI-AKI. However, only 15/24 actually specifically mention to measure serum creatinine before contrast administration. Different thresholds of estimated glomerular filtration rate (eGFR) are used to define clinically significant CKD. Most commonly an eGFR of <60 mL/min is used. Some guidance documents add that patients with an eGFR of <30 mL/min have a still higher risk, and the KDIGO guidelines state that especially the population with an eGFR of <45 mL/min is at risk. As other risk factors, the following were mentioned: age (N = 14/24), concurrent use of nephrotoxic medication (N = 14/24), presence of cardiovascular disease (N = 18/24) and diabetes (N = 18/24). Some other risk factors were discussed, but these were not always mentioned in all guidelines.

FIGURE 1: Scores for the different guidance documents for the different domains of AGREE-II.

1. ACCI/AHA [14]
2. ACR [15]
3. NICE [16]
4. ESICM [17]
5. UK-RI, BCS, RCR [18]
6. ACR-SPR [19]
7. RAND/CIHR [20]
8. Catheterisation and Cardiovascular interventions [21]
9. ACR [33]
10. KDIGO [13]
11. Mayo Clinic [22]
12. NXTI [34]
13. CAR [23]
15. ESUR [25]
factors were mentioned in different guidance documents, such as dehydration, haemodynamic instability, volume and dose of applied contrast, intra-arterial versus intravenous contrast administration, sepsis and multiple myeloma. Although the total volume of the given contrast is considered a risk factor, none of the guidance documents identified that different commercial contrast agents have different iodine concentrations and can thus differ in absolute amount of contrast for the same volume administered. (Supplementary data, Table S2).

Although all guidance documents recommended prophylactic volume expansion (Supplementary data, Table S3), there were differing views on the total volume, infusion rate, type of solution and timing of the fluid administration. Only six guidance documents consider the use of the oral route for fluid administration, and only two specifically recommend this route for patients at lower risk.

Almost all guidelines noted that low- and iso-osmolar contrast media carry a lower risk for CI-AKI as compared with high-osmolar contrast media. Older guidelines suggest a lower risk for CI-AKI for iso-osmolar versus low-osmolar contrast media, whereas more recent guidelines state that there is no difference in risk, based mainly on more recent evidence from randomised controlled trials. None of the guidance documents recommends N-acetylcysteine as sole measure, but 10/24 consider it a potentially useful additional measure. The administration of NaHCO₃ is advised in 15/24 of the guidance documents.

**DISCUSSION**

Our evaluation of guidance documents on the prevention of CI-AKI revealed a wide consensus on the need for pre-hydration in patients at risk for CI-AKI. There was however no clear consensus on the definition of patients at risk (i.e. definition of the target population that should receive preventive measures). Recommendations on how to achieve adequate pre-hydration also varied widely in total volume, timing and nature of fluid administration (saline or bicarbonate), and only few guidance documents mentioned the possibility of the oral route for pre-hydration. Regarding the osmolality of contrast medium, earlier guidelines have a greater tendency to recommend low-osmolar or iso-osmolar solutions, whereas, based on accumulating evidence, more recent guidelines only recommend to avoid hypertonic media in high-risk patients. There is wide agreement that N-acetylcysteine is not sufficient as sole preventive measure. Only three guidance documents were considered to be of sufficient quality. Further, our review reveals that only the KDIGO [13] and NICE guidance documents [16] provide tools for implementing the recommendations in a sustainable and efficient way. Both guidelines discuss the existence of risk prediction models of CI-AKI, and the NICE guideline [16] even assesses their validity. NICE [16] developed extensive tools for incorporating guidance into practice, including a baseline assessment to help guideline users planning activity that will help meet the recommendations, a costing statement, audit tools and slide sets.

**Definition of CI-AKI**

It is remarkable that one out of three guideline articles surveyed does not even offer a straightforward definition of CI-AKI. In the remaining papers, the proposed definitions vary. Strictly defining the population, the nature of the intervention and basis for comparison is one of the key stages for systematic reviewing and guidance production. Failure to do this can result in violating the internal and external validity of the guideline [12]. In our review, the exact definition of CI-AKI is fundamental for the scope of the guideline and for defining the population at risk and the possible underlying risk factors. In 1999, the European Society of Urogenital Radiology defined contrast nephropathy as an increment in serum creatinine level of >25% compared with baseline within 2–5 days following the administration of iodinated contrast media [37]. This definition was used in many clinical trials, sometimes adding an absolute increase in serum creatinine of >0.5 mg/dL as a criterion. In 32% of the guidelines, this definition is still being used. There is accumulating evidence that many risk factors, preventive measures and the immediate and long-term prognosis of the kidney problems related to contrast media are shared by other causes of AKI. Consequently, the KDIGO guidelines on contrast-induced AKI stated that there are no pathophysiological or epidemiological reasons why the definition and staging of CI-AKI should be different from the RIFLE/AKIN criteria [13]. Most of the recent guidelines accept this definition and by applying this common definition and staging, CI-AKI studies should allow valid comparison among different clinical trials in the future.

**Identification of patients at risk**

The incidence of CI-AKI varies depending on the patient population and the applied definition. In patients with a normal renal function (even in the presence of diabetes), which includes the vast majority of the patients undergoing radiologic procedures with administration of contrast, the risk for CI-AKI is minimal (1–2%). In high-risk populations, the risk may be as high as 25% [6]. Identifying at-risk patients is therefore the cornerstone of efficient CI-AKI prevention. However, our review illustrates that there is no standard definition for what constitutes an ‘at-risk’ patient. The primary factor on which the guidelines agree is the presence of pre-existing CKD. However, also here, differing thresholds are used, leaving no solid basis for the clinician to identify ‘patients at risk’. Such a failure to identify the target population that should benefit from preventive measures for CI-AKI can have serious logistical consequences on the practical implementation of the guidance. For example, guidance documents recommending preventive measures in patients with an eGFR of <60 versus <30 mL/min will result in much higher patient numbers needing pre-hydration, and thus more expenses and logistical challenges. It is in this regard also remarkable that only 60% of the guidance documents advise to actually measure serum creatinine prior to all contrast-enhanced procedures to identify patients at risk. On the other hand, several authors question the feasibility of implementing such a strategy, as this would require the ambulatory patient to make an additional medical visit to determine the
eGFR. An acceptable time interval between the determination of eGFR and contrast administration in the ambulatory patient at risk for CI-AKI is almost never defined. Few guidelines mention the use of questionnaires for identifying patients at risk or the use of dipstick testing for proteinuria as a marker of CKD.

Guidelines disagree on relevant secondary risk factors, such as diabetes, age, concomitant use of other nephrotoxic agents and underlying vascular disease.

Quality of provided guidance

We found that all assessed guidelines had significant shortcomings, warranting future efforts for improving methods both to develop new guidelines and to assess the quality of existing ones. This conclusion was already made by Alonso-Coello et al. [8] after an evaluation of 42 AGREE evaluations published between 1980 and 2007. In their study, the lowest scores were attributed to the domains ‘stakeholder involvement’, ‘applicability’ and ‘editorial independence’.

In general, most guidelines in our review received a very low score for applicability/implementability, with scores for this domain ranging from 10 to 56% and a mean score of 24% with only one guideline scoring >50%. Failure to address the issue of implementation and to provide clear, practical advice can have important consequences. For example, all guideline authors agree that extracellular volume expansion by intravenous salt and fluid loading can help in preventing CI-AKI in the population at risk. However, none of the guidance documents consider the logistical difficulties in implementing this recommendation in specific patient groups. In practice, ambulatory patients need to come to a day care clinic or may even need hospitalization to receive intravenous fluids, with substantial consequences for health care budgets. Since in clinical practice the recommended infusion regimens mostly consist of pre-loading before the actual contrast application and post-loading thereafter, contrast investigations in ambulatory patients at risk for CI-AKI need to be planned either in the late morning or the early afternoon, allowing sufficient time for the infusion.

From a health economic point of view, reducing the number of hospitalizations for prevention of CI-AKI could yield an important cost-reduction. It is therefore surprising that few guidance documents investigated the question whether increasing oral fluid and salt intake could be a valid alternative for IV fluid administration. Apparently, the evidence seems to indicate that both are equally effective, provided that patients actually do drink the salted solutions [38]. The ERBP guideline [26], an adaptation of the KDIGO guideline [13], is one of the few guidelines mentioning the use of oral hydration. As it is crucial that patients drink the prescribed salted solution, adequate patient information leaflets or tools on the importance of pre-hydration in avoiding CI-AKI need to be provided. However, none of the guidelines seem to emphasize this practical but important point or provide suggestions on how pre-hydration could actually be done by the oral route. The NICE guideline [16] obtained the highest score in the area of ‘stakeholder involvement’ by explicitly involving patients and patient representatives in their guideline development groups and is the only guideline stating that ‘oral fluids may be preferable to patients’. It also recognises that the need for hospital admissions could yield an important cost impact and suggest therefore using shorter fluid regimens for elective day case procedures. Most guidelines also remain rather vague on which hydration regimen actually needs to be used and only one-third of them offer a regimen that can be easily implemented in clinical practice. Furthermore, few guidelines suggest how to ensure that patients at risk are identified in time so that pre-hydration can be offered to them and patients at risk are potentially being overlooked. The KDIGO guidelines [13] and the European Society of Urogenital Radiology guidelines [25] are the only ones to offer a risk-factor model to identify patients with pre-existing kidney disease without need for a serum creatinine measurement. Additionally, most of the guidelines extrapolate findings of inadequately controlled observational studies on intra-arterial administrated contrast to the intravenous use of contrast. Despite some caveats regarding selection bias and possible underrepresentation of patients with severe renal impairment, several publications suggest that the incidence of CI-AKI after intravenous administration of contrast may be overestimated. Few guidelines even differentiate between these two situations [39–41].

The guidelines assessed in our review obtained very low scores for the domains ‘editorial independence’ and ‘rigour of development’. The wide variability observed in these scores is worrying, since these domains directly reflect the reliability of the guidelines. The low scores may be due to actual problems in guideline development, but because of the nature of the AGREE scoring, they may also simply be due to insufficient clarity and communication of the process used. The influence of insufficient editorial independence may best be reflected in the choice of type and volume of contrast being used. Nowadays, high-osmolar contrast media are rarely used in modern radiology units, since randomized clinical trials already showed that they result in higher prevalence of CI-AKI, compared with iso- or low-osmolar contrast media. Between 2000 and 2010, there was a tendency towards using iso-osmolar contrast media, as they were believed to be superior in the prevention of CI-AKI, especially in high-risk patients. These older guidelines however have a low score for ‘methodological rigour’ and ‘editorial independence’. In the 2007 guideline of the American College of Cardiology Foundation/American Heart Association, iso-osmolar contrast in patients with CKD undergoing angiography was promoted [14]. However, since then, accumulating evidence from randomized controlled trials failed to support the superiority of iso-osmolar contrast media. As a consequence, more recent and more methodologically sound guidelines no longer recommend iso-osmolar over low-osmolar contrast agents. This change in preference illustrates the impact of ‘methodological rigour’ and ‘editorial independence’. It also underlines that differences in recommendations can be due to changes in available evidence. Therefore, there is a strong need for regular updates of clinical practice guidelines [42]. Twice a year, the American College of Cardiology for example reviews the available evidence for their guidelines on the management of patients with unstable angina NSTEMI and issues updates on an as-needed base [14]. Most guidance documents, however, fail to clarify their strategy or plans for producing updates, although a recent study showed that in general, one out of
five recommendations is outdated 3 years after publication [42]. Failure to provide a strategy for updating guidelines can result in ad hoc adaptations rather than systematic improvements. New studies, if positive (i.e. those that find that a new intervention is more effective), are more likely to result in an adaptation of the guideline, whereas negative studies do not result in the correction of an existing recommendation.

Of note, the only recent guideline that promotes the use of the more expensive iso-osmolar contrast for high-risk patients is the one with the lowest score for ‘rigour of development’ [34]. Furthermore, the risk of CI-AKI increases with the amount of contrast applied, and most guidance documents therefore recommend using a volume as low as possible to obtain good quality images. Only the ACCF/AHA guidelines [14] suggest calculating the contrast volume to creatinine clearance ratio to define the maximum contrast volumes that can be administered without significantly increasing the baseline risk of CI-AKI. However, concentrations of iodine vary between different contrast solutions, and none give a method for calculating maximum recommended volumes for contrast solutions taking into account variability in iodine concentration. This all exemplifies that, besides methodological rigour, there is also a need for creative reflection and judicious, Socratic-like discussion in the guideline development group on what the questions and evidence at hand fundamentally are, regarding the desired outcomes one has in mind. It is clear that avoidance of conflicts of interest and including as many different stakeholders as possible is necessary to obtain such an open-minded discussion, allowing all potential facets of the problem to be identified.

Guidelines are mostly perceived as unbiased, evidence-based and valid, and yet, there are important differences in the recommendations given in the evaluated guidance documents. Often, the underlying evidence is weak or not applicable to the population specified in the guideline. Clinical experts are needed to translate available evidence into recommendations [43]. Furthermore, guideline users can benefit from explicit systems to rank the quality of evidence suitable to a specific clinical context and explicitly link them to the supporting evidence. Earlier studies showed that these grading systems are seldom used.

Some of the appraised guidelines focus on specific clinical situations (e.g. critically ill patients, with a higher risk on CI-AKI) and a limitation of the AGREE-II instrument may be that this aspect is not taken into account.

Additionally, our investigation seems to support the statement that guideline development benefits from the input of methodologists and economists [44, 45].

**CONCLUSION**

Our review of available guidance documents on the prevention of CI-AKI reveals that only 3 out of 15 were of sufficient methodological quality. However, even in these three documents, important gaps remain regarding ‘stakeholder involvement’ and ‘applicability’. Whereas there is consensus that pre-hydration is necessary, there is no consensus on whom should receive pre-hydration, neither on how this pre-hydration should be executed in clinical practice. This might result in unnecessary treatment in some and missed opportunities for prevention in other patients. Critical reflection is warranted when transferring the provided guidance into a local standardized operating protocol.

**SUPPLEMENTARY DATA**

Supplementary data are available online at http://ndt.oxfordjournals.org.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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