Chapter 23. Interventions To Prevent Contrast-Induced Acute Kidney Injury

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How Important Is the Problem?

Over 70 million computed tomography (CT) scans are performed yearly in the United States,¹ approximately half of which use iodinated radiocontrast media, and over 2 million patients undergo other studies using radiocontrast media such as coronary angiograms.² Contrast-induced acute kidney injury (CI-AKI) is one of the major risks of procedures using radiocontrast media. CI-AKI is generally defined by laboratory criteria: biochemical CI-AKI is usually defined as an increase in serum creatinine of 25%, or an absolute increase of 0.5 mg/dl, within 2-5 days after receiving contrast.³ A prospective study⁴ found that the incidence of CI-AKI by this definition was 7.7% in patients with impaired baseline kidney function (defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m²), ranging from 6.5% in patients undergoing CT scans to 13.2% in patients undergoing non-coronary angiography.

Risk factors for CI-AKI include chronic kidney disease (CKD) of any cause, especially in diabetic patients. Other risk factors include intravascular volume depletion and disease states associated with decreased effective circulating volume and renal perfusion, such as congestive heart failure (CHF) and liver failure, and concomitant use of nephrotoxic medications, particularly non-steroidal anti-inflammatory drugs (NSAIDs).⁵ Procedural risk factors also play a role, with larger volumes of contrast media, intra-arterial contrast administration (such as in coronary angiography), and use of high-osmolarity contrast media all independently associated with elevated risk for CI-AKI. Patients with normal baseline kidney function have minimal risk of CI-AKI.

Although biochemical CI-AKI is commonly documented, the link between laboratory abnormalities and clinical outcomes is controversial. Several studies have shown an independent link between CI-AKI diagnosis in hospitalized patients and subsequent increases in length of stay,⁶ progression to end-stage renal disease,⁷ and short- and long-term mortality.⁸ However, causality is difficult to determine despite the presence of this association, because many factors that predispose to CI-AKI (especially CHF and CKD) also are associated with adverse clinical outcomes independent of CI-AKI development. In addition, AKI of any cause is associated with worsened short- and long-term outcomes in hospitalized patients.⁹ In prospective studies, CI-AKI has been found as an asymptomatic laboratory abnormality in the vast majority of patients. Only 1 of 660 patients in a 2008 study by Weisbord et al.⁴ required kidney dialysis after receiving contrast.

What Is the Patient Safety Practice?

The standard of care to prevent CI-AKI includes several widely accepted, evidence-based interventions:

- Intravascular volume expansion with intravenous normal saline¹⁰
- Limiting the volume of contrast administered
• Avoidance of high-osmolar contrast media in patients with impaired baseline renal function
• Stopping nephrotoxic medications, especially NSAIDs

Published guidelines from the American College of Radiology, the European Society of Radiology, and the Canadian Association of Radiology all recommend the above measures. The original review of this topic for Making Health Care Safer (2001) also recommended volume expansion with normal saline and avoidance of high-osmolar contrast. The 2009 American College of Cardiology/American Heart Associated guidelines for percutaneous coronary interventions also recommend avoidance of high-osmolar contrast media.

In addition to standard care, several interventions have been widely studied to prevent CI-AKI. These practices are the focus of this review:
• Volume expansion with intravenous sodium bicarbonate
• Administration of n-acetylcysteine
• Use of iso-osmolar (instead of low- or high-osmolar) contrast media
• Prophylactic renal replacement therapy (dialysis)
• Administration of HMG CoA-reductase inhibitors ("statins")

Why Should This Patient Safety Practice Work?
The pathophysiology of CI-AKI is complex and incompletely understood. Intravascular contrast administration is thought to induce renal vasoconstriction, which may lead to medullary ischemia, particularly in the presence of intravascular volume depletion or other medications that may cause afferent renal artery vasoconstriction such as NSAIDs. Contrast media, particularly older high-osmolar media, may be directly toxic to the renal tubules. Finally, some component of renal damage is thought to be mediated by generation of reactive oxygen species ("free radicals"). Because patients suspected of suffering CI-AKI rarely undergo kidney biopsy for definitive diagnosis, the relative contribution of these mechanisms is unclear. As a result, the mechanisms by which the proposed PSPs prevent CI-AKI are also somewhat speculative.

Opportunities for improving CI-AKI prevention definitely exist, as studies show that appropriate and proven prophylactic interventions are not universally applied. Studies have found that volume expansion is used in only 40% of at-risk patients undergoing coronary angiography and 60% of patients undergoing computed tomography. In the latter study, only 7% of patients had nephrotoxic medications discontinued.

What Are the Beneficial Effects of the Patient Safety Practice?
We designed a structured literature search with the assistance of a medical librarian to identify studies of interventions to prevent CI-AKI. Searching PubMed identified 193 randomized controlled trials and 53 meta-analyses of various interventions to prevent CI-AKI published in the past 10 years. (Searching of the Cochrane Controlled Trials Registry and the Cochrane Database of Systematic Reviews did not identify any additional trials.) In contrast, the original Making Health Care Safer report published in 2001 identified only 10 RCTs and 1 meta-analysis.

Based on the expansion in this literature, we opted to conduct a systematic meta-review of the meta-analyses of CI-AKI prevention published since January 1, 2007. We chose this inclusion date based on prior literature demonstrating that the results of systematic reviews are
generally not stable by 5 years after publication. The revised search identified 32 studies, of which 20 were confirmed to be meta-analyses after full-text review (the others were largely narrative reviews). These 20 meta-analyses evaluated the effectiveness of 5 distinct interventions for preventing CI-AKI:

- Hydration with intravenous sodium bicarbonate (N=11)\textsuperscript{16-26}
- Administration of oral N-acetylcysteine (NAC, N=3)\textsuperscript{27-29}
- Use of iso-osmolar radiocontrast media (N=3)\textsuperscript{30-32}
- Prophylactic renal replacement therapy (RRT, N=1)\textsuperscript{33}
- Administration of HMG CoA-reductase inhibitors (statins, N=1)\textsuperscript{34}

In addition, one study\textsuperscript{35} evaluated the combination of NAC and bicarbonate in preventing CI-AKI compared with NAC alone.

We followed the methodology previously outlined by Whitlock\textsuperscript{36} for incorporating previously published systematic reviews into a new review. Each identified review was evaluated for quality using the AMSTAR checklist\textsuperscript{37}, and information was extracted on the interventions and outcomes assessed, the study populations (including the types of radiologic studies for which contrast media was used) and sample size, the definition of CI-AKI used, and the overall conclusions of the review (Table 1).

**Hydration With Intravenous Sodium Bicarbonate**

We identified a total of 11 meta-analyses published since 2007\textsuperscript{16-26} comparing sodium bicarbonate hydration to volume expansion with normal saline. These meta-analyses all used the same definition of CI-AKI (a 25% increase in the serum creatinine level, or an absolute increase of $\geq 0.5$ mg/dl, within 2-5 days of the procedure).

The review with the most recent inclusion date\textsuperscript{19} completed its search through February 2009, and identified a total of 18 published and unpublished trials. This meta-analysis was methodologically sound, scoring 11 (of a possible 11) on the AMSTAR scale, and overall found a slight benefit for bicarbonate compared with saline volume expansion in preventing CI-AKI by the laboratory definition (pooled OR 0.66, 95% CI 0.45-0.95). There was no reported improvement in the need for renal replacement therapy or mortality. This seemingly positive result was tempered by numerous caveats. The authors noted significant heterogeneity across included trials, found evidence for publication bias, and considered the quality of included trials to be low. Therefore, the authors concluded “only a limited recommendation can be made in favour of sodium bicarbonate.”

Another meta-analysis with a slightly earlier study inclusion date of December 2008\textsuperscript{25} actually included more trials (N=23, including 14 unpublished trials). This meta-analysis also scored 11 on the AMSTAR scale. The pooled trial results found evidence for a slight benefit for bicarbonate compared with saline volume expansion in preventing laboratory-defined CI-AKI (pooled relative risk 0.62, 95% CI 0.45 to 0.86). However, the authors performed a meta-regression analysis and found that bicarbonate was effective only in smaller, poor-quality trials. Larger, higher-quality trials generally found neutral results. This meta-analysis, which appears to be the most comprehensive study of bicarbonate prophylaxis for CI-AKI, concludes that “the effectiveness of sodium bicarbonate treatment to prevent contrast-induced nephropathy remains unclear.”

The other 9 meta-analyses identified in our search did not include any other trials (published or unpublished) that were not included in the 2 meta-analyses discussed above. Significant
heterogeneity was found in all 11 meta-analyses, and all of the meta-analyses that included unpublished studies found evidence of publication bias.

Therefore, we conclude that sodium bicarbonate therapy appears to offer only marginal benefit at best over routine saline volume expansion, and the primary literature suffers from significant limitations. Routine bicarbonate administration cannot be recommended to prevent CI-AKI.

Administration of Oral N-Acetylcysteine

The role of N-acetylcysteine in CI-AKI prevention has been quite thoroughly studied. We identified 3 meta-analyses published since 2007\(^\text{27-29}\), but prior to 2007 an additional 12 meta-analyses and 2 meta-reviews had already been published. Limitations in the prior literature—and the meta-analyses of this literature—have been well documented; in fact, a 2006 meta-review\(^\text{38}\) described the plethora of NAC trials and meta-analyses as “a case study in the pitfalls of the evolution of evidence”. No consensus on the effectiveness of NAC existed as of 2007, as the existing meta-analyses produced differing results.

The most recent meta-analysis of interventions included randomized controlled trials published through February 2008\(^\text{29}\) and evaluated only studies of high-dose NAC protocols (defined as administration of \(>1,200\)mg/day of oral NAC or a single periprocedural dose of \(>600\)mg) compared with saline volume expansion. This high-quality meta-analysis (AMSTAR score of 11) found that high-dose NAC protocols were effective in preventing biochemically defined CI-AKI (random effect odds ratio 0.52; 95% CI, 0.34 to 0.78) in a trial population predominantly composed of patients undergoing coronary angiography. This meta-analysis did not extract or report information on clinical outcomes. However, a large RCT\(^\text{39}\) that was published after this review and also used a high-dose NAC protocol did not find any reduction in biochemical CI-AKI, need for hemodialysis, or mortality in patients undergoing coronary angiography. This study enrolled 2,308 patients, whereas the 16 RCTs included in the meta-analysis in total enrolled only 1,677 patients.

Another earlier meta-analysis that included trials published through March 2006\(^\text{28}\) identified 26 trials of NAC, using different dosing regimens ranging from 400 mg/day to 1,200 mg/day. This meta-analysis did find evidence for a significant reduction in biochemically defined CI-AKI. However, there was significant unresolved heterogeneity in this study. The meta-analysis published by Gonzales et al.\(^\text{27}\), which included all but 6 of the same studies, noted that evidence of benefit was confined to a small group of relatively low-quality studies which showed very large relative benefits from NAC. These studies were also performed and published earlier than subsequent larger, higher-quality trials that reported negative results.

Based on these findings, we conclude that routine use of NAC at any dose does not appear to convincingly reduce the incidence of CI-AKI. As with bicarbonate infusion, there is no evidence that NAC administration decreases the incidence of clinically meaningful outcomes such as the need for renal replacement therapy.

Use of Iso-Osmolar Contrast Media

There are three types of iodinated radiocontrast media: high-osmolar, low-osmolar, and iso-osmolar. High-osmolar contrast is little used due to its nephrotoxic effects, and low-osmolar contrast media has become the standard of care. So-called iso-osmolar contrast has an even lower osmolality than “low-osmolar” contrast, and 3 meta-analyses\(^\text{30-32}\) have evaluated the renoprotective effect of the iso-osmolar contrast medium iodixanol compared with low-osmolar
contrast media (LOCM, of which there are several agents). The most recent and largest meta-analysis identified 36 randomized controlled trials published before December 2009. This meta-analysis was high quality, scoring 11 on the AMSTAR scale. It did not find a statistically significant reduction in biochemical CI-AKI for iso-osmolar contrast compared with all LOCM agents (pooled OR 0.77, 95% CI 0.56 to 1.06). However, a subgroup analysis did find that iso-osmolar contrast was associated with a reduction in CI-AKI in studies comparing iodixanol to one specific low-osmolar agent, iohexol (pooled OR 0.25, 95% CI 0.11-0.55, N=10 trials). This finding was also noted in the other two meta-analyses of this question. None of the meta-analyses evaluated the effect of iso-osmolar contrast media on clinical outcomes.

Other than this advantage of iodixanol over the specific agent iohexol, there is therefore no convincing evidence supporting the routine use of iso-osmolar contrast. The 2009 ACC/AHA guidelines for percutaneous coronary intervention recommend use of iso-osmolar contrast or use of LOCM other than iohexol. This is a change from the 2007 guidelines, which specifically recommended use of iso-osmolar agents.

**Prophylactic Renal Replacement Therapy**
One meta-analysis analyzed 9 RCTs evaluating the effectiveness of prophylactic renal replacement therapy (RRT) on prevention of biochemically defined CI-AKI, need for long-term RRT, and mortality. The patients included in the individual studies uniformly had baseline kidney dysfunction (at least stage 3 chronic kidney dysfunction, with baseline serum creatinines ranging from 1.5 to 4.2 across the studies). Overall, prophylactic RRT was not associated with decreased biochemical CI-AKI or the need for long-term hemodialysis. The authors did find a statistically significant reduction in mortality associated with prophylactic RRT (RR 0.33, 95% CI 0.11 to 0.77), but the significance of this finding is quite questionable given the lack of effect on the primary outcome. The authors speculated that the mortality benefit might instead represent a general benefit of RRT in critically ill patients with AKI.

**Administration of Statins**
One recent meta-analysis identified 6 small RCT’s evaluating the effect of statins on biochemical CI-AKI. There was no overall beneficial effect of statins on prevention of CI-AKI.

**Coadministration of Bicarbonate and N-Acetylcysteine**
One meta-analysis identified 10 RCT’s that studied the effectiveness of combination of bicarbonate and NAC compared with NAC alone. The authors reported a reduction in biochemical CI-AKI with combination therapy, but the result did not reach statistical significance (pooled RR 0.65, 95% CI 0.40 to 1.05), nor did combination therapy reduce the incidence of renal failure requiring dialysis.

**What Are the Harms of the Patient Safety Practice?**
The individual interventions that have been evaluated to prevent CI-AKI are generally considered low risk. Bicarbonate and NAC are not associated with a significant risk of clinically relevant adverse effects, and likewise, iso-osmolar contrast media do not have a unique side effect profile compared with other routinely used radioc contrast agents. The exception is renal replacement therapy, which requires placement of large bore central venous access, exposing patients to complications of this procedure including hemorrhage, pneumothorax, or central line-associated bloodstream infections.
One potential harm is that administration of intravenous fluids may increase the risk of clinically significant congestive heart failure (CHF) in patients with a known diagnosis of CHF. However, the largest meta-analysis of intravenous bicarbonate administration did not find an increased incidence of symptomatic CHF.25

How Has the Patient Safety Practice Been Implemented, and in What Contexts?

Interventions to prevent CI-AKI have been studied in patients with a range of risk factors for CI-AKI, and have included patients with no preexisting renal dysfunction as well as those with chronic kidney disease. Studies have also assessed patients undergoing a variety of radiologic procedures, including those associated with a higher risk of CI-AKI such as coronary angiography. Within specific interventions, there are a range of specific protocols used for administering prophylactic medications. However, across all the meta-analyses of this subject, no unique subgroup of patients has been identified that benefits from any specific intervention.

At the health care system level, some steps have been taken to implement protocols to minimize the risk of CI-AKI. Brown et al.40 conducted a mixed-methods study of CI-AKI prevention practices at 10 centers enrolled in the Northern New England Cardiovascular Disease Study Group PCI Registry. The incidence of biochemically defined CI-AKI varied widely across sites, ranging from 1.9% to 10% even after adjustment for covariates. The two centers with the lowest CI-AKI rates both had strong clinical leadership that prioritized CI-AKI prevention and utilized standardized protocols for volume administration, NAC administration, and minimizing the time that patients were NPO prior to procedures. Interestingly, one of these centers used normal saline and the other bicarbonate for volume administration, indicating that the choice of fluid likely matters less than ensuring that patients receive adequate volume prior to the procedure.

Are There Any Data About Costs of the Patient Safety Practice?

We did not identify any formal cost-effectiveness analyses of the various modalities proposed to prevent CI-AKI published since 2007. Interventions such as bicarbonate and NAC are low cost, whereas iso-osmolar contrast media (IOCM) is more costly than standard LOCM. One cost-effectiveness analysis demonstrated that IOCM is cost-effective compared with LOCM,41 but this analysis was based on earlier, more favorable estimates of the benefits of IOCM that have not been borne out in subsequent trials or meta-analyses. We also identified one cost-effectiveness analysis of prophylactic RRT published in 2006,42 which found that prophylactic RRT might be cost-effective only in a subset of patients with stage 4 chronic kidney disease. This analysis was also based on favorable treatment estimates that have not been confirmed in formal systematic reviews.

Are There Any Data About the Effect of Context on Effectiveness?

There is no definitive evidence that any single intervention to prevent CI-AKI is more effective in specific patient populations (e.g., patients with more advanced chronic kidney disease) or undergoing specific radiologic procedures (e.g., patients undergoing intra-arterial contrast procedures such as coronary angiography versus patients undergoing procedures requiring intravenous contrast. Health care system factors have not been studied as an effect modifier for specific CI-AKI preventive interventions.
Conclusions and Comment

We identified 20 meta-analyses testing various interventions to prevent CI-AKI. However, despite this intensive research, we were unable to identify any unique interventions that clearly are effective at preventing either biochemical CI-AKI or clinically relevant outcomes such as renal failure requiring hemodialysis. Moreover, even the significance of biochemical evidence of kidney injury after contrast is debated, and some experts question the importance of this as a proxy measure or target for intervention. At this point, it appears that standard therapy, most importantly volume administration with intravenous normal saline prior to procedures, is the most efficacious method of preventing CI-AKI. Use of standardized CI-AKI prevention protocols that emphasize volume administration may be associated with a lower risk of CI-AKI in patients undergoing coronary angiography. A summary table is located below (Table 1).

Table 1, Chapter 23. Summary table

<table>
<thead>
<tr>
<th>Scope of the Problem Targeted by the PSP (Frequency/Severity)</th>
<th>Strength of Evidence for Effectiveness of the PSPs</th>
<th>Evidence or Potential for Harmful Unintended Consequences</th>
<th>Estimate of Cost</th>
<th>Implementation Issues: How Much do We Know?/How Hard Is it?</th>
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<td>Common/Low</td>
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<td>Negligible</td>
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References


