

Prevention of Contrast-Induced Nephropathy in the Emergency Department

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Study objective: Contrast-induced nephropathy is the third leading cause of hospital-acquired acute renal failure. Expanded use of contrast-enhanced imaging exposes an ever-widening number of patients to this renal toxin. We perform an evidence-based emergency medicine review comparing different therapies to prevent contrast-induced nephropathy. We limit our review to prophylactic therapies that are practical for an emergency department setting.

Methods: We searched MEDLINE, EMBASE, and the Cochrane Library for randomized trials comparing a wide range of medications to prevent contrast-induced nephropathy. We defined contrast-induced nephropathy by a commonly used surrogate measure of renal failure: a 25% or 0.5 mg/dL absolute increase in serum creatinine level from baseline 48 to 72 hours postcontrast. We limited our review to only trials for patients with baseline renal insufficiency, who are most at risk for contrast-induced nephropathy. We excluded prophylactic protocols requiring more than 2 hours precontrast to initiate and any trials of experimental medications or those that required invasive monitoring. We used standard criteria to appraise the quality of published trials.

Results: We found 7 randomized trials; 3 using *N*-acetylcysteine, 2 using theophylline, and 1 each using bicarbonate and ascorbic acid. Although many of these trials showed statistically significant reductions in the risk for contrast-induced nephropathy, none were sufficiently powered to detect reductions in mortality rate or the need for dialytic therapy.

Conclusion: Evidence from randomized trials shows that these interventions (theophylline, bicarbonate, and ascorbic acid) under review were appropriate to an ED setting and decreased the risk of contrast-induced nephropathy. The case for the effectiveness (*N*-acetylcysteine) was less certain. [Ann Emerg Med. 2007;50:335-345.]

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CLINICAL SCENARIO

A 78-year-old black hypertensive woman with type II diabetes mellitus is brought to your emergency department (ED) by ambulance. The paramedics state that the patient was getting dressed this morning and had a syncopal episode witnessed by family members. She reports a sharp, tearing chest pain radiating to her scapula that woke her from sleep. As part of her evaluation, a contrast-enhanced computed tomography (CT) scan of her chest is ordered to rule out thoracic aortic dissection. Routine laboratory tests are reported as blood urea nitrogen 12.2 mg/dL and creatinine level 2.0 mg/dL. As you are ordering the CT angiogram of the chest, the radiology technician tells you that you must get approval for all contrast-enhanced CT studies for patients with serum creatinine levels greater than 1.5 mg/dL. The radiologist on call tells you that patients can have significant renal insufficiency with serum

creatinine levels even within normal limits. This patient's increased creatinine level places her at risk for renal failure from intravenous contrast agents. The radiologist goes on to say that perhaps you should provide pretreatment with prophylactic *N*-acetylcysteine before this contrast study. The patient is treated with hydration and the *N*-acetylcysteine protocol recommended by the radiologist. After your shift, you decide to examine the evidence that any prophylactic therapy for contrast-induced nephropathy would be effective, given the time and resource constraints in a busy ED. The following evidence-based emergency medicine review seeks an answer to the question posed by this scenario.¹

FORMULATING THE QUESTION

In formulating the question for this review, we were interested in which protocols prevented the direct patient harms

associated with postcontrast nephropathy. We initially focused our review of contrast-induced nephropathy on the need for dialysis and mortality. We quickly realized that need for dialysis and mortality associated with contrast administration were rare in the general population. McCullough et al² have estimated that the prevalence of acute renal failure requiring dialysis after contrast tests was less than 1%, with an even lower mortality rate, which has made the study of these rare patient-centered outcome variables not feasible from a sample size prospective. Instead of using these patient-oriented outcomes, most studies define contrast-induced nephropathy according to decrements in renal function as measured by small increases of serum creatinine level from baseline soon after contrast administration. Contrast-induced nephropathy is generally defined by a proportional rise of 25% in serum creatinine level or an absolute increase in serum creatinine level by 0.5 mg/dL from baseline 48 hours after contrast exposure.^{3,4}

There is abundant justification for this use of small changes in serum creatinine level as a surrogate endpoint to define contrast-induced nephropathy. Once renal function has been affected by contrast media, emergency dialysis will be required for 14%² to 35%⁵ of patients, with 2%² to 19%⁶ of these people requiring long-term hemodialysis. Patients with any degree of renal insufficiency from contrast media have longer hospital stays, with higher mortality rates, which range from 7.1%² to 14.9%⁵ and increases to more than 35%² if patients require hemodialysis.

These dire consequences from an exclusively iatrogenic cause of acute renal failure have led to this conservative definition of contrast-induced nephropathy. Because almost all studies of contrast-induced nephropathy use this definition, we have adopted this surrogate measure of postcontrast nephropathy for this review.

Even using this conservative definition of contrast-induced nephropathy, its prevalence in the general patient population is still low, between 0.7%⁷ and 3.3%.⁸ Most contrast-induced nephropathy patients rapidly recover renal function in 3 to 7 days, with less than 1% of all coronary angiography patients progressing onto dialysis.² Although these facts should provide us with some comfort in ordering contrast studies in the majority of our patients, patients with baseline renal insufficiency are at a particularly high risk for contrast-induced nephropathy. Patients with precontrast serum creatinine level greater than their hospital's upper limit of normal or patients with an estimated glomerular filtration rate less than 60 mL per minute per 1.73 m² have a prevalence of contrast-induced nephropathy greater than 30%.^{2,5,8}

Because a large number of agents and treatment protocols have been proposed as means for preventing contrast-induced nephropathy, we elected to consider a broad range of potential interventions, provided that they conform to the period of emergency care and do not require intensive monitoring. Our detailed clinical question is therefore: In patients with baseline renal insufficiency (increased serum creatinine level or an

estimated glomerular filtration rate below 60 mL/minute/1.73 m²), which interventions within 2 hours or less of the study and not requiring invasive or intensive monitoring prevent contrast-induced nephropathy? We also reviewed these studies to see whether these interventions prevented need for dialysis and decreased mortality associated with contrast-induced nephropathy.

SEARCHING FOR AND SELECTING THE BEST EVIDENCE

We included all studies of patients with baseline renal insufficiency who were older than 18 years and receiving radiocontrast agents. We excluded studies testing agents not readily available in most EDs (therefore excluding experimental or very expensive medications) and therapies with a high potential for adverse complications (therefore excluding many of the antihypertensive medications). We also excluded trials according to the practicality of carrying out these interventions in a busy ED, which removed medications that required intensive monitoring of the patient for changes in blood pressure or cardiac rhythm.

We chose to review only protocols that could be initiated up to 2 hours before contrast administration because of the practical time constraints of working in most EDs. Although the limit was somewhat arbitrary, we chose a 2-hour limit because, in our experience, this was the longest acceptable delay in obtaining a contrast CT. This 2-hour limit would allow sufficient time for laboratory result turnaround and ingestion and gastrointestinal transit of oral contrast.

We searched for randomized trials and systematic reviews of interventions to prevent contrast-induced nephropathy in patients with baseline renal insufficiency. Although our clinical scenario refers to a patient receiving intravenous contrast for a CT scan, we decided to include trials to prevent contrast-induced nephropathy in patients after arteriography of either the peripheral or coronary arteries, which was a practicality because the majority of contrast-induced nephropathy prophylaxis studies were conducted in patients undergoing coronary angiography. Yet the difference between venous and arterial contrast injection may have important implications for the risk of contrast-induced nephropathy. Arteriography generally requires larger contrast volumes than CT scans, which increases the probability of nephropathy.⁹ In addition, this higher risk of contrast-induced nephropathy is compounded in arteriography by higher concentrations of the contrast agent going directly to the kidneys compared to dilution of contrast in total blood volume after intravenous injection. In addition, the placement of an arterial catheter runs the added risk of renal failure from cholesterol emboli.¹⁰

We searched MEDLINE with the PubMed interface from 1966 to December 2005 and EMBASE from 1980 to January 2006 with the Ovid Technologies interface (see Appendix E1, available online at <http://www.annemergmed.com>, for complete MEDLINE and EMBASE search strategies).

Our search yielded 512 results. We also searched Cochrane Libraries for completed systematic reviews and protocols through 2005. These databases did not yield any further articles. We reviewed the bibliographies of eligible trials and systematic reviews and selected narrative reviews and editorials for citations and additional eligible articles. This search yielded an additional 9 articles, bringing the final total of eligible articles to 521. We excluded 503 of these articles because the intervention was not initiated within 2 hours of contrast administration, leaving a total of 16 articles for consideration.

We further excluded another 9 trials. Interventions using dopamine^{11,12} or fenoldopam^{13,14} were excluded because these medications require continuous blood pressure monitoring, not usually available for the general ED patient population. We excluded interventions using nifedipine,¹⁵ felodipine,¹⁶ and furosemide¹⁷ from our review because of the risk of using antihypertensive agents in a general emergency medicine population. The study by Weinstein et al¹⁸ using furosemide was excluded for lack of randomization, concealment, and blinding. This study used a large dose of furosemide (average 110 mg intravenous) that resulted in higher rates of contrast-induced nephropathy. We also excluded atrial natriuretic peptide¹⁸ because of concerns raised by recent retrospective reviews, which found a decrease in creatinine clearance¹⁹ and an increase in short-term mortality rate²⁰ associated with this medication. Finally, we excluded experimental agents such as endothelin receptor antagonists²¹ and L-arginine²² or prohibitively expensive agents such as prostaglandin E.²³

Application of our inclusion and exclusion criteria yielded 7 studies that directly addressed our clinical question: 3 involved *N*-acetylcysteine,²⁴⁻²⁶ 2 used theophylline,^{27,28} and 1 each administered bicarbonate²⁹ and ascorbic acid.³⁰

DESCRIPTION OF THE TRIALS

Table 1 summarizes the key elements of the 7 randomized trials included in our review. Three trials (Ochoa et al,²⁴ Baker et al,²⁵ and Durham et al²⁶) tested *N*-acetylcysteine in patients who had baseline renal insufficiency and were receiving contrast for coronary angiography. Both Ochoa et al²⁴ and Durham et al²⁶ used the same hydration protocol in intervention and comparison groups. It seems that Baker et al²⁵ administered the standard precontrast hydration protocol to patients in the control group only. All 3 *N*-acetylcysteine protocols were initiated at the most 1 hour before contrast administration. Only Baker et al²⁵ used a weight-based intravenous *N*-acetylcysteine dose (150 mg/kg), which resulted in significantly larger *N*-acetylcysteine dosages, whereas Ochoa et al²⁴ and Durham et al²⁶ used fixed oral *N*-acetylcysteine doses of 1,000 mg and 1,200 mg, respectively. All *N*-acetylcysteine protocols gave a follow-up dose between 3 and 4 hours after the initial treatment.

Huber et al^{27,28} conducted 2 consecutive trials of theophylline in renal insufficiency patients. Huber et al²⁷ first studied patients receiving intravenous contrast for a variety of radiologic studies (coronary angiography, iliofemoral

arteriography, computed tomography, etc).²⁷ A second study was restricted to subjects scheduled for coronary angiography.²⁸ It was not clear whether the latter study²⁸ included some of the cardiac catheterization patients contained in the first study.²⁷ Both studies used the same prehydration scheme in their controls and intervention groups. The dose and route of theophylline (200 mg IV) given 30 minutes before contrast administration were the same for both studies. Neither study protocol required a repeated dose of theophylline. The remaining 2 trials studied individual protocols using bicarbonate²⁹ and ascorbic acid.³⁰

The inclusion criteria for all the trials were patients with precontrast renal insufficiency. The wide range of definitions of baseline renal insufficiency between the trials is an important source of variability between these studies. Five of the trials²⁶⁻³⁰ defined renal insufficiency solely by a baseline serum creatinine level greater than a stated lower limit, which varied between 1.1 and 1.7 mg/dL. None of these trials described the method by which their clinical laboratory measured creatinine level, which introduces another source of variability between the trials because different methods for measuring serum creatinine level result in divergent upper limits of normal values, leading to the inclusion of patients possibly without significant renal insufficiency.³¹

Ochoa et al²⁴ did not specify the contrast agent used in their study. Durham et al²⁶ and Baker et al²⁵ limited their trial to patients exposed only to a nonionic iso-osmolar contrast agent. Spargias et al,³⁰ Huber et al,^{27,28} and Merten et al²⁹ had a protocol only with nonionic low-osmolar agents.

The use of some concomitant medications has the potential to increase the risk of contrast-induced nephropathy, including nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors through their inhibition of vasodilating prostaglandins^{32,33} and atrial natriuretic peptide and diuretics as a result of their potential to decrease blood volume.³⁴ Of our 7 trials under review, only 3^{24,25,29} were careful to exclude or limit the use of concomitant medications in their study patients.

Table 2 summarizes our assessment of the likelihood of bias within the 7 reported trials. Although randomization was stated in all 7 trials, only studies by Durham et al,²⁶ Merten et al,²⁹ and Spargias et al³⁰ expressly detailed the randomization methodology and had adequate concealment.

Blinding of patients and physicians to the intervention was adequate in all studies, except for Baker et al,²⁵ in which the hydration protocols were significantly different between intervention and control groups.

Complete follow-up of study patients until their 48-hour postcontrast serum creatinine level test occurred only in the trials by Huber et al.^{27,28} The remainder of the trials failed to completely follow up all enrolled patients, which presents a potentially serious problem in the interpretation of their results. Given the low event rates in the included trials, even a loss of 2% to 3% of patients could significantly affect the study results. Only the trials by Merten et al²⁹ and Spargias et al³⁰ identified

Table 1. Summarizing the characteristics of the 7 trials under review.

Studies	Patient Population	Intervention	Comparison	Outcomes
Ochoa et al, 2004 ²⁴	Inclusion criteria: Cr >1.8 mg/dL (male patients) or Cr >1.6 mg/dL (female patients) or CrCl <50 cc/min Exclusion criteria: Decompensated congestive heart recent cardiogenic shock or vasopressors, suspected severe aortic stenosis, or recent initiation of diuretics or ACEI Contrast agent: Agent and dose varied.	NAC 1,000 mg PO 1 h precontrast and 4 h postcontrast Hydration: NS 4 h before and 6 h postcontrast	Hydration: NS 150 mL/h; 4 h pre- and 6 h postcontrast	CIN: Increase in serum creatinine level of 0.5 mg/d or an increase in serum creatinine level by 25% at 48 h postcontrast
Baker et al, 2003 ²⁵	Inclusion criteria: Cr >1.36 mg/dL or an estimated CrCl < 50 mL/min Exclusion criteria: NSAIDs, systolic blood pressure 90 mm Hg or hemodynamically significant valvular heart disease Contrast agent: Isotonic, nonionic contrast medium	NAC 150 mg/kg in 500 mL NS during 30 min precontrast and 50 mg/kg in 500 mL NS over 4 h postcontrast.	Hydration: NS 1 mL/kg/h 12 h pre- and postcontrast.	CIN defined as an increase in serum creatinine by 25% at either 48 or 96 h postcontrast
Durham et al, 2002 ²⁶	Inclusion criteria: Cr >1.7 mg/dL Exclusion criteria: Patients <18 y, reversible renal disease, atheroembolic disease, severe asthma, breast feeding, severe peptic ulcer disease, or respiratory disease Contrast agent: Isotonic, nonionic contrast medium.	NAC 1,200 mg 1 h precontrast and a second dose 3 h postcontrast Hydration: ½ NS was given at 1 mL/kg/h for 12 h pre- and postcontrast.	Hydration: ½ NS 1 mL/kg/h of 12 h pre- and postcontrast exposure.	CIN defined as an increase in serum creatinine level of 0.5 mg/d at 48 h postcontrast
Merten et al, 2004 ²⁹	Inclusion criteria: Cr >1.1 mg/dL Exclusion criteria: Severe or recent or ESRD, uncontrolled HTN, pregnancy, or recent use of dopamine, mannitol or fenoldopam Contrast agent: Nonionic low osmolality	NaHCO ₃ 154 mEq/L NaHCO ₃ in D5W 1,000 cc at 3 mL/kg per h for 1 h precontrast and 1 mL/kg per h during the contrast exposure and 6 h postcontrast	Hydration: 154 mEq/L of NaCl in 5% D5W same rate and timing as NaHCO ₃ solution.	CIN: Increase in serum creatinine level of 0.5 mg/d or an increase in serum creatinine by 25% at 48 h postcontrast
Huber et al, 2003 ²⁷	Inclusion criteria: Cr >1.3 mg/dL Exclusion criteria: Pregnancy or seizures, arrhythmia or Lown classification >IVa Contrast agent: Nonionic low osmolality	Theophylline 200 mg in 100 mL NS IV 30 min precontrast Hydration: Suggested intake 2 L/dY	Hydration: Suggested intake 2 L/dY	CIN defined as an increase in serum creatinine level of 0.5 mg/d at 48 h postcontrast
Huber et al, 2002 ²⁸	Inclusion criteria: Cr >1.3 mg/dL Exclusion criteria: Pregnancy or seizures, arrhythmia or Lown classification >IVa Contrast agent: Nonionic low osmolality	Theophylline 200 mg in 100 mL NS IV 30 min precontrast Hydration: Suggested intake 2 L/day	Hydration: Suggested intake 2 L/day	CIN defined as an increase in serum creatinine level of 0.5 mg/d at 48 h postcontrast
Spargias et al, 2004 ³⁰	Inclusion criteria: Cr >1.2 mg/dL Exclusion criteria: Severe or recent or ESRD Contrast agent: Nonionic low osmolality	Ascorbic acid 3 g PO 2 h precontrast and 2 g the night of and the morning after the procedure Hydration: NS at 50–125 cc/h starting at least 2 h precontrast and continued for 6 h.	Hydration: NS at 50–125 cc/h starting at least 2 h precontrast and continued for 6 h.	CIN: Increase in serum creatinine level of 0.5 mg/d or an increase in serum creatinine by 25% at 2–5 days postcontrast

Cr, serum creatinine; mg/dL, milligram per decilitre; CrCl, estimated creatinine clearance; cc/min, cubic centimetres per minute; ACEI, angiotensin-converting enzyme inhibitor; NAC, N-acetylcysteine; PO, post operation; h, hour; NS, normal saline solution (0.9%); mL/h, milliliter per hour; CIN, contrast-induced nephropathy; mg/D, milligrams per day; mL/min, milliliter per minute; NSAIDs, nonsteroidal anti-inflammatory drugs; mm Hg, millimeters of mercury; mg/kg, milligrams per kilograms; y, year; ESRD, end-stage renal disease; HTN, hypertension; NaHCO₃, sodium hydrogen carbonate; D5W, dextrose 5% water; L/dY, liters per day.

how many of the patients lost to follow-up were either in the control or interventions groups. Spargias et al³⁰ conducted the only trial in which a sensitivity analysis was conducted with the patients lost to follow-up. In this sensitivity analysis, 1 contrast-induced nephropathy outcome was added to both the control and intervention arms, and the results did not change.

RESULTS OF THE TRIALS

Table 3 summarizes the results of the trials under review in terms of the occurrence of contrast-induced nephropathy between the intervention and comparison groups. None of the trials we reviewed were of sufficient power to study the effect of their prophylactic measures in preventing renal failure requiring

Table 2. Summarizing the assessment for susceptibility to important bias of the 7 reported trials.

	Randomization	Concealment	Intention to Treat	Baseline Comparisons	Blinding	Cointerventions	Completeness Follow-up
Ochoa et al, 2004, ²⁴ NAC	Single-center randomized trial; randomization protocol unspecified	Unclear	Yes	Well balanced for risk factors for CIN	Treatment assignment blinded to patients and providers. Intervention and Placebo in same oral diluent but not tested for equivalence of taste and appearance.	Similar hydration protocols in both intervention and comparison groups	24% Of patients had incomplete data sets, unclear as to their division between intervention or comparison groups.
Baker et al, 2003, ²⁵ NAC	Multicenter randomized trial, randomization protocol unspecified	Unclear	Yes	Well balanced for risk factors for CIN	Unblinded	Different hydration protocols for intervention and comparison groups.	5% Of patients had incomplete data sets, unclear as to their division between intervention or comparison groups.
Durham et al, 2002, ²⁶ NAC	Single-center randomized trial, assigned by the pharmacy according to a computer-generated schedule	Adequate	Yes	Well balanced for risk factors for CIN	Treatment assignment blinded to patients, providers, and assessors.	Similar hydration protocols in both intervention and comparison groups	2 Patients (2.5%) had incomplete data sets, unclear as to their division between intervention or comparison groups.
Merten et al, 2004, ²⁹ bicarbonate	Single-center randomization assigned by the pharmacy according to a computer-generated schedule	Adequate	Yes	Well balanced for risk factors for CIN	Treatment assignment blinded to patients, providers, and assessors	Similar hydration protocols in both intervention and comparison groups	7% Of patients lost to follow-up were excluded from analysis. Post hoc sensitivity analysis did not change primary result.
Huber et al, 2003, ²⁷ theophylline	Single-center randomized trial; randomization protocol unspecified.	Unclear	Yes	Well balanced for risk factors for CIN	Unclear	Hydration protocols not specified. Hydration volumes not measured for either experimental group.	Yes
Huber et al, 2002, ²⁸ theophylline	Single-center randomized trial; randomization protocol unspecified.	Unclear	Yes	Well balanced for risk factors for CIN	Double blinded, but the identities of those who were blinded not specified	Hydration protocols not specified. Hydration volumes not measured for either experimental group.	Yes
Spargias et al, 2004, ³⁰ ascorbic acid	Single center; randomization was in blocks of 10.	Adequate	Yes	Well balanced for risk factors for CIN	Treatment assignment blinded to physicians, but blinding of patients unspecified. Placebo not tested for equivalence of taste and appearance.	Similar hydration protocols in both intervention and comparison groups	3% Of patients lost to follow-up were excluded from analysis. Post hoc sensitivity analysis did not change primary result.

Table 3. Results of studies to prevent contrast-induced nephropathy.

Study	Total (n)	Risk for CIN	RR for Intervention (95% CI)	NNT (95% CI)
Ochoa et al, 2004 ²⁴				
NAC	80	3/36 (8%)	0.33 (0.10–1.04)	NA
Normal saline solution		11/44 (25%)		
Baker et al, 2003 ²⁵				
NAC	80	2/41 (5%)	0.24 (0.06–0.91)	6.4 (4.4–88)
Normal saline solution		8/39 (20%)		
Durham et al, 2002 ²⁶				
NAC	79	10/38 (26%)	1.20 (0.55–2.60)	NA
Normal saline solution		9/41 (22%)		
Merten et al, 2004 ²⁹				
Bicarbonate	119	1/60 (2%)	0.12 (0.015–0.72)	8.4 (6.8–40)
Normal saline solution		8/59 (14%)		
Huber et al, 2002 ²⁸				
Theophylline	100	2/50 (4%)	0.25 (0.06–0.97)	8.3 (5.6–414)
Oral hydration		8/50 (16%)		
Huber et al, 2003 ²⁷				
Theophylline	100	2/50 (4%)	0.20 (0.05%–0.75)	6.3 (4.6–29.6)
Oral hydration		10/50 (20%)		
Spargias et al, 2004 ³⁰				
Ascorbic acid	231	11/118 (9%)	0.46 (0.24–0.88)	9.1 (5.4–52.7)
Normal saline solution		23/113 (20%)		

NA, Not applicable; NNT, number needed to treat; RR, relative risk.

dialytic therapy. Studies by Huber et al^{27,28} and Spargias et al³⁰ did not explicitly state whether they followed up patients to ascertain which, if any, required dialysis. Ochoa et al²⁴ followed up patients for 30 days without finding any patients who required dialysis. Baker et al²⁵ and Durham et al²⁶ followed up patients only during the length of their hospitalization. Baker et al²⁵ found no incidences of patients requiring dialysis, and Durham et al²⁶ observed that 2 patients received hemodialysis but did not state whether these patients were in the intervention or comparison groups.

Durham et al²⁶ and Ochoa et al²⁴ found no significant difference in the rates of contrast-induced nephropathy between their comparison and intervention groups. The Figure is a Forest plot of the relative risks of contrast-induced nephropathy, which shows significant overlap in all of the reviewed trials.

The definition of the primary outcome variable, contrast-induced nephropathy, was not consistent between the studies. This heterogeneity among study outcomes may explain the observed variability in their baseline contrast-induced nephropathy event rates (14% to 25%). McCullough et al,² in a study of 1,826 cardiac catheterization patients, found that the prevalence of contrast-induced nephropathy varied with its definition. Using a definition of contrast-induced nephropathy requiring only a 25% proportional increase from baseline creatinine level resulted in a 14.5% prevalence of contrast-

induced nephropathy. Yet a more stringent definition of contrast-induced nephropathy of an absolute increase of 0.5 mg/dL produced a much lower contrast-induced nephropathy prevalence of only 3.9%. Of our reviewed trials, only Durham et al²⁶ used the most conservative definition of contrast-induced nephropathy (absolute increase in serum creatinine level by 0.5 mg/dL) and failed to show any benefit with their intervention. This more stringent definition of contrast-induced nephropathy may have been balanced by a higher innate risk of renal failure in this trial because both the intervention and controls groups had higher baseline serum creatinine level than did any of the other studies. Spargias et al³⁰ reanalyzed their data with different definitions of contrast-induced nephropathy and found a statistically significant difference between intervention and control groups only with the application of the least stringent definition of their outcome measure (25% proportional increase of serum creatinine level). When Spargias et al³⁰ used a more stringent definition of contrast-induced nephropathy (absolute increase of serum creatinine level >0.5 mg/dL), no significant benefit to their intervention was observed.

Baker et al,²⁵ Merten et al,²⁹ and both studies by Huber et al^{27,28} used only a proportional (25%) increase in serum creatinine level and found a statistically significant decrease in nephropathy with their respective interventions. Ochoa et al²⁴ defined contrast-induced nephropathy by using either criterion.

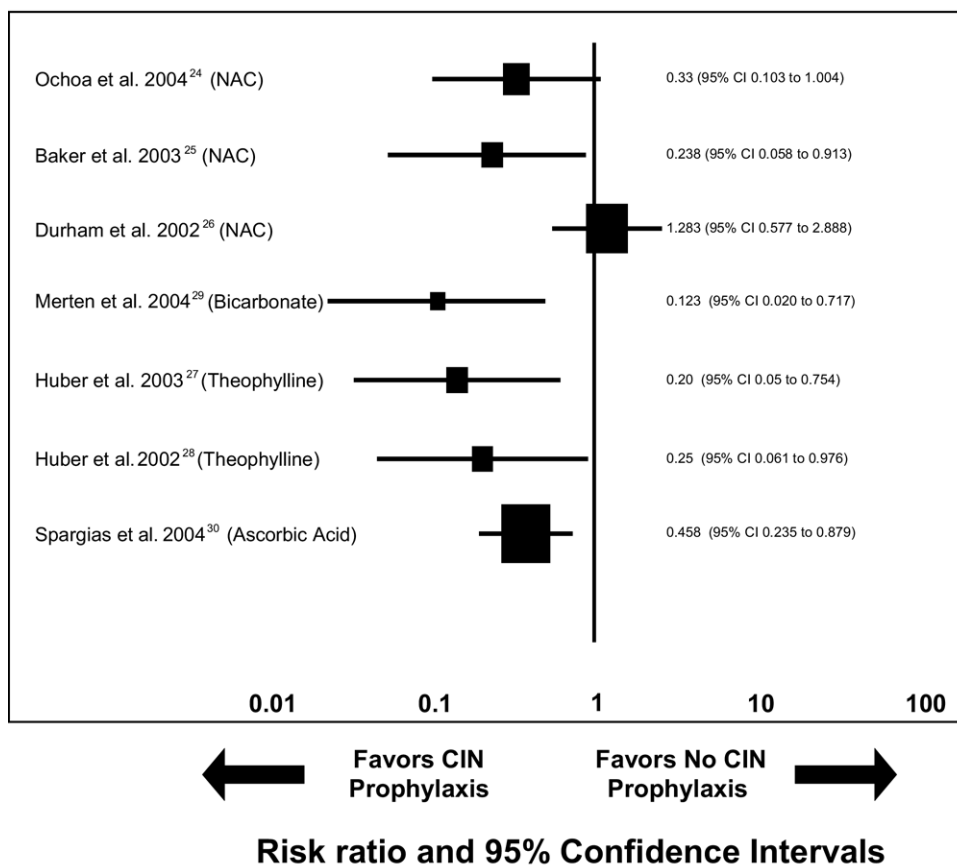


Figure. Forest plot of outcome of contrast-induced nephropathy. For each trial, the small square corresponds to the observed relative risk for contrast-induced nephropathy, and the horizontal line represents the 95% CIs. A relative risk of 1, identified by the vertical line, occurs when the effect is equivalent for the intervention and comparison therapy. *CIN*, Contrast-induced nephropathy; *NAC*, *N*-acetylcysteine.

The inconsistency of each study's definition of contrast-induced nephropathy may explain some of the between-study variability.

Both Ochoa et al²⁴ and Durham et al²⁶ found no complications related to *N*-acetylcysteine therapy, whereas Baker et al²⁵ found that 14.6% of their patients experienced transitory allergic reactions. Theophylline pretreatment was associated with only a small increase in pulse (>15 beats/min) in the earlier article by Huber et al.²⁸ Complications of bicarbonate therapy²⁹ were limited to an increase in blood pressure after fluid infusion in both the intervention and comparison groups. The trial of ascorbic acid³⁰ did not discuss complications of this therapy.

APPLYING THE EVIDENCE

From the [Figure](#), trials using theophylline, bicarbonate, and ascorbic acid clearly demonstrate a decreased incidence of contrast-induced nephropathy. Yet the 95% confidence intervals (CIs) for their respective relative risks overlap, signifying no one superior prophylactic measure. For *N*-acetylcysteine, the results are mixed. Only the *N*-acetylcysteine trial by Baker et al²⁵ showed a lower incidence of contrast-

induced nephropathy, whereas larger studies by Ochoa et al²⁴ and Durham et al²⁶ failed to prove any benefit to *N*-acetylcysteine. Durham et al,²⁶ who conducted the largest trial, even showed a trend toward a higher incidence of contrast-induced nephropathy after *N*-acetylcysteine administration.

This question remains for this review: is a proportional (25%) or absolute (0.5 mg/dL) increase in serum creatinine level an appropriate surrogate for the more clinically important outcomes of contrast-induced nephropathy such as progressive renal failure, requirements for dialysis, or higher mortality rates? A surrogate outcome is defined as a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how the patient feels, functions, or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.³⁵ Unfortunately, it has been said that a correlate does not a surrogate make.³⁶

It has been estimated that contrast-induced nephropathy is the third leading cause of acute renal failure in hospitalized patients.³⁷ Maydoon et al³⁸ reported that up to 30% of contrast-induced nephropathy patients go on to have permanent

decreases in renal function. The more severe the precontrast renal insufficiency, especially when complicated by diabetes, the greater the risk for developing renal failure requiring dialysis. In patients with a precontrast creatinine clearance less than 10 mL per minute, 84% of diabetics required dialysis compared to only 48% of the nondiabetic subjects.²

Besides renal insufficiency as a risk for contrast-induced nephropathy, different contrast agents have various risks of nephropathy. Contrast media are divided into 2 broad categories: ionic and nonionic. The nonionic agents have lower risks of contrast-induced nephropathy, especially in renal insufficiency patients.³⁹ Nonionic contrast media are further subdivided by their osmolality into high, low, and iso-osmolar categories. Contrast-induced nephropathy is less likely to develop in high-risk patients after the use of iso-osmolar compared to high- and low-osmolar nonionic contrast media.⁴⁰

Mortality rates after contrast-induced nephropathy range from 7.1%² to 14.9%⁵ and increase as much as 35%² if the patients require dialysis. In a more complex review of contrast-induced nephropathy mortality rates, Levy et al⁴¹ compared in-hospital mortality rates of 183 critically ill patient who developed contrast-induced nephropathy matched with 174 similarly ill patients who did not develop contrast-induced nephropathy. These patients were evenly matched for age and sex. Before adjustment for comorbidities, the mortality rate for contrast-induced nephropathy patients was 34% compared with only 7% in those without contrast-induced nephropathy. After adjustment for comorbidities, contrast-induced nephropathy was still associated with an increased risk of death (odds ratio [OR] 5.5). Deaths from renal failure (acidosis, fluid overload, hyperkalemia) were rare; most contrast-induced-nephropathy patients who died had sepsis, bleeding, or respiratory failure.

None of the trials we reviewed compared mortality rates between their intervention and comparison groups. Recently, Marenzi et al⁴² showed a significantly lower in-hospital mortality rate in patients when *N*-acetylcysteine successfully prevented contrast-induced nephropathy compared to controls. The prevalence of contrast-induced nephropathy in their high-dose *N*-acetylcysteine group (8%) was significantly ($P < .001$) lower than that of their controls (33%). This higher rate of contrast-induced nephropathy in their controls was associated with a significantly higher OR (5.43; 95% CI 1.24 to 23.81) of dying compared with their high-dose *N*-acetylcysteine group. Unfortunately, this study included subjects with and without baseline renal insufficiency, so we could not formally include it in our review, which was restricted to only patients with baseline renal insufficiency.

Although contrast-induced nephropathy is relatively uncommon, once diagnosed, 35% of patients will require in-hospital dialysis,⁵ 19% will go on to long-term renal replacement,⁶ and approximately 15% will die.⁵ It seems from these experiences in cardiac patients with contrast-induced nephropathy that prevention of renal failure is a reasonable goal. Comparing complications from contrast-induced nephropathy

in a diverse group of cardiac patients to an equally varied group of ED patients has yet to be done. Until these comparison studies are done, it may be justified in using the complication rates of cardiac patients to examine the potential benefits in prophylaxing ED patients against contrast-induced nephropathy.

According to the results of the 7 trials we reviewed (Table 3), the number needed to treat to prevent 1 excess case of contrast-induced nephropathy ranged from 6 to 9. If we then combine this estimate of number needed to treat with the complications of contrast-induced nephropathy from cardiac patients, we can estimate the number needed to treat to prevent dialysis requirements and mortality. Compared to hydration alone, any of the agents in our 7 trials will have an estimated number needed to treat of 26, and possibly more than about 150, to prevent 1 excess case of contrast-induced nephropathy requiring in-hospital dialysis; a number needed to treat of 47, and possibly more than about 250, to prevent 1 case with chronic end-stage renal failure; and finally a number needed to treat of 60, and possibly more than about 400, to prevent 1 death. We expect the number needed to treat for ED patients to be even higher than coronary angiography patients, who have inherently greater risks for renal failure and death. Although these numbers needed to treat seem large, they must be balanced by the fact that these agents at the doses and rates studied have an excellent safety profile.

The best way to prevent contrast-induced nephropathy is first to recognize the potential risks for contrast-induced nephropathy in your patients. We recommend caution when administering contrast to elderly patients (>70 years), diabetic patients, those receiving concomitant nephrotoxic agents (nonsteroidal antiinflammatory agents and diuretics), and those with renal insufficiency.⁴³ In patients at risk for contrast-induced nephropathy, the most effective measure to prevent nephropathy is obviously to avoid contrast administration. If contrast is unavoidable, then adequate volume resuscitation is not controversial.⁴⁴

This elderly (>75 years old) diabetic patient with renal insufficiency (creatinine level >2.0 mg/dL) has significant risks for developing contrast-induced nephropathy and its inherent complications. Using a contrast-induced nephropathy risk score developed by Mehran et al⁴³ (Appendix E2, available online at <http://www.annemergmed.com>), we estimate our patient to have a risk of renal damage of greater than 25% and greater than 1% risk of requiring dialysis. The radiologist's recommendation that a prophylactic agent be offered before our patient's contrast-enhanced imaging study is consistent with this estimation. Within the period of emergency care, the evidence seems to most consistently favor theophylline, bicarbonate, or ascorbic acid, with the latter 2 particularly compelling in view of their safety profile.

PATIENT COMMUNICATION

"We are recommending that you undergo a test to help us decide whether you have a serious condition causing your

symptoms. The test requires administration by vein of a chemical that could put stress on your kidneys. In a small number of patients, this stress can progress to major renal damage, requiring dialysis. The risk is increased when there are signs of kidney weakness in blood tests or in someone with diabetes. Several treatments are available that have been shown in scientific studies to reduce this risk, but the number of patients that benefit from them is small. The treatments are safe but may cause a 1- to 2-hour delay in doing the test and in making the diagnosis.”

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Critically Appraised Topic (CAT): What interventions are available to prevent the renal failure and death associated with contrast-induced nephropathy?

Question In patients with baseline renal insufficiency, which interventions are effective in preventing contrast-induced nephropathy and its complications, given the resource and time constraints in a busy ED?

Reviewed by Sinert RH, Doty C

Date of search December 2005

Expiration date July 2008

Clinical bottom line Evidence from randomized trials shows that these interventions (theophylline, bicarbonate, and ascorbic acid) under review were appropriate to an ED setting and decreased the risk of contrast-induced nephropathy. The case for the effectiveness (N-acetylcysteine) was less certain.

Search strategy MEDLINE, EMBASE, the Cochrane Library from the dates of origin through June of 2006.

Citations **Primary: 7 fully reported randomized trials**

- Ochoa A, Pellizzon G, Addala S, et al. Abbreviated dosing of N-acetylcysteine prevents contrast-induced nephropathy after elective and urgent coronary angiography and intervention. *J Interv Cardiol.* 2004;17:159-165.
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Primary study characteristics

Study Population

Patients with baseline renal insufficiency, older than 18 years, and receiving radiocontrast agents.

Interventions

N-acetylcysteine: 3 Studies

Theophylline: 2 Studies

Bicarbonate: 1 Study

Ascorbic acid: 1 Study

Outcome Measures

Contrast-induced nephropathy was defined by either a proportional increase of 25% in serum creatinine level or an absolute increase in serum creatinine level by 0.5 mg/dL from baseline 48 h after contrast exposure. In addition, we reviewed each trial for changes in the rates of renal failure requiring in-hospital dialysis and death between intervention and control groups.

Fair to good quality was observed in all 7 trials.

Critical appraisal

Results

Primary and secondary outcomes

5 of the 7 studies found a statistically significant lower incidence of contrast-induced nephropathy in their intervention compared to their control groups. There was important heterogeneity among the trials using NAC, with the largest trial displaying a trend favoring control.

Intervention	# Studies	Relative Risk of Contrast-Induced Nephropathy Intervention vs Comparison (95% CIs)
N-acetylcysteine	3	0.33 (0.10 to 1.0) 0.24 (0.06 to 0.9) 1.28 (0.58 to 2.9)
Theophylline	2	0.25 (0.06 to 0.97) 0.20 (0.05 to 0.75)
Bicarbonate	1	0.12 (0.015 to 0.72)
Ascorbic acid	1	0.46 (0.24 to 0.88)

No study was sufficiently powered to detect significant improvements in mortality rate or the rate of renal failure requiring dialysis with their interventions.

APPENDIX E1. DESIGN SEARCH STRATEGY.
MEDLINE (PubMed) 1966 to June 2006

1. "Contrast Media"[MeSH]
2. "Contrast Media"[Pharmacological Action]
3. (contrast media) OR (contrast medium) OR
4. #1 OR #2 OR #3
5. "Kidney Diseases"[MeSH]
6. nephritis OR nephropath* OR nephrotoxic*
7. (renal insufficiency)
8. (Contrast induced nephr*) OR (Contrast a
9. #5 OR #6 OR #7 OR #8
10. #4 AND #9
11. ("Clinical Trial"[Publication Type] OR "Clinical Trials" [MeSH])
12. ("Randomized Controlled Trials"[MeSH] OR "Randomized Controlled Trial"[Publication Type])
13. random*
14. placebo
15. (singl* OR doubl* OR tripl*) near (mask* or blind*)
16. sham
17. #11 OR #12 OR #13 OR #14 OR #15 OR #16
18. #10 AND #17
19. "Humans"[MeSH]
20. #18 AND #19

Note: * denotes truncation; tw, text word; pt, publication type.

EMBASE 1966 to June 2006

1. exp Contrast Medium/
2. ((contrast adj media) or (contrast adj medium) or (contrast adj dye) or (radiographic adj contrast)).tw.
3. ((radiocontrast adj media) or (radiocontrast adj medium) or (contrast adj agent\$)).tw.
4. or/1-3
5. exp Kidney Disease/
6. (nephritis or nephropath\$ or nephrotoxic\$).tw.
7. ((impair\$ adj5 renal) or (impair\$ adj5 kidney) or (damag\$ adj5 renal) or (damag\$ adj5 kidney) or (reduc\$ adj5 renal) or (reduc\$ adj5 kidney)).tw.
8. (renal adj insufficiency).tw.
9. ((contrast adj induced adj nephr\$) or (contrast adj associated next nephr\$)).tw.
10. or/5-9
11. 4 and 10
12. Clinical Trial/
13. Randomized Controlled Trial/
14. random\$.tw.
15. placebo\$.tw.
16. ((sing\$ or doubl\$ or tripl\$) adj (masked or blind\$)).tw.
17. sham\$.tw.
18. or/12-17
19. 11 and 18
20. Limit 19 to human

APPENDIX E2.

Risk assessment for contrast-induced nephropathy.⁴³

Risk Factors	IntegerScore
Hypotension*	5
Intraarterial balloon pump	5
Congestive heart failure†	5
Age >75 y	4
Anemia‡	3
Diabetes	3
Contrast media volume	1 For each 100 mL
Serum creatinine level >1.5 mg/dL or Estimate GFR§	4 2 for 40–60 mL/min/1.73 m ² 4 for 20–40 mL/min/1.73 m ² 6 for <20 mL/min/1.73 m ²

*Hypotension: systolic blood pressure <80 mm Hg.

†CHF: Class III-IV by New York Heart Association criteria or history of pulmonary edema.

‡Anemia: Hematocrit level <39% for men and <36% for women.

§Estimated GFR by Modification of Disease in Renal Disease formula.

Scoring system for risk of contrast-induced nephropathy.

Risk Score	Risk of Contrast-Induced Nephropathy, %	Risk of Dialysis, %
0–6	7.5	0.04
6–10	14.0	0.12
11–16	26.1	1.09
>16	57.3	12.8