



**MICHAEL R. RUDNICK, MD\***

Associate Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia

**AARON KESSELHEIM, MD**

Brigham and Women's Hospital, Boston

**STANLEY GOLDFARB, MD†**

Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia

# Contrast-induced nephropathy: How it develops, how to prevent it

## ■ ABSTRACT

No current treatment can reverse or ameliorate contrast-induced nephropathy once it occurs, but prophylaxis is possible. Many preventive measures have failed to show benefits in well-designed, prospective, randomized, double-blinded trials. This review will focus only on the prophylactic strategies that have possible or proven value.

## ■ KEY POINTS

The risk of contrast-induced nephropathy is directly proportional to the severity of preexisting renal insufficiency.

Hydration with normal saline solution is the most widely accepted preventive intervention.

*N*-acetylcysteine may be effective, but studies have given conflicting results.

Sodium bicarbonate may be of value, but larger multicenter studies are needed to determine its true effectiveness.

Newer contrast agents that are nonionic and of lower osmolality than older agents are less nephrotoxic but can still cause nephropathy.

Due to the logistical effort and high cost associated with hemofiltration, larger randomized trials should be performed before this technique can be recommended as standard prophylaxis against contrast-induced nephropathy in high-risk patients.

Theophylline cannot yet be recommended as standard prophylaxis against contrast-induced nephropathy.

**M**UCH REMAINS TO BE DETERMINED about contrast-induced nephropathy, ie, the acute renal failure that sometimes develops after giving iodinated radiocontrast agents. For example:

- What causes it? The short answer seems to be renal ischemia, but via what pathways? Are contrast agents directly nephrotoxic?
- How can it be prevented, short of not using contrast? Many agents that looked good in theory have proved useless. Hydration seems to be a good principle, but what is the best prescription? Must it be intravenous, or will oral hydration suffice? Is sodium bicarbonate better than sodium chloride as an intravenous hydration solution?
- Is the latest iso-osmolar agent better than the low-osmolar agents currently in use?

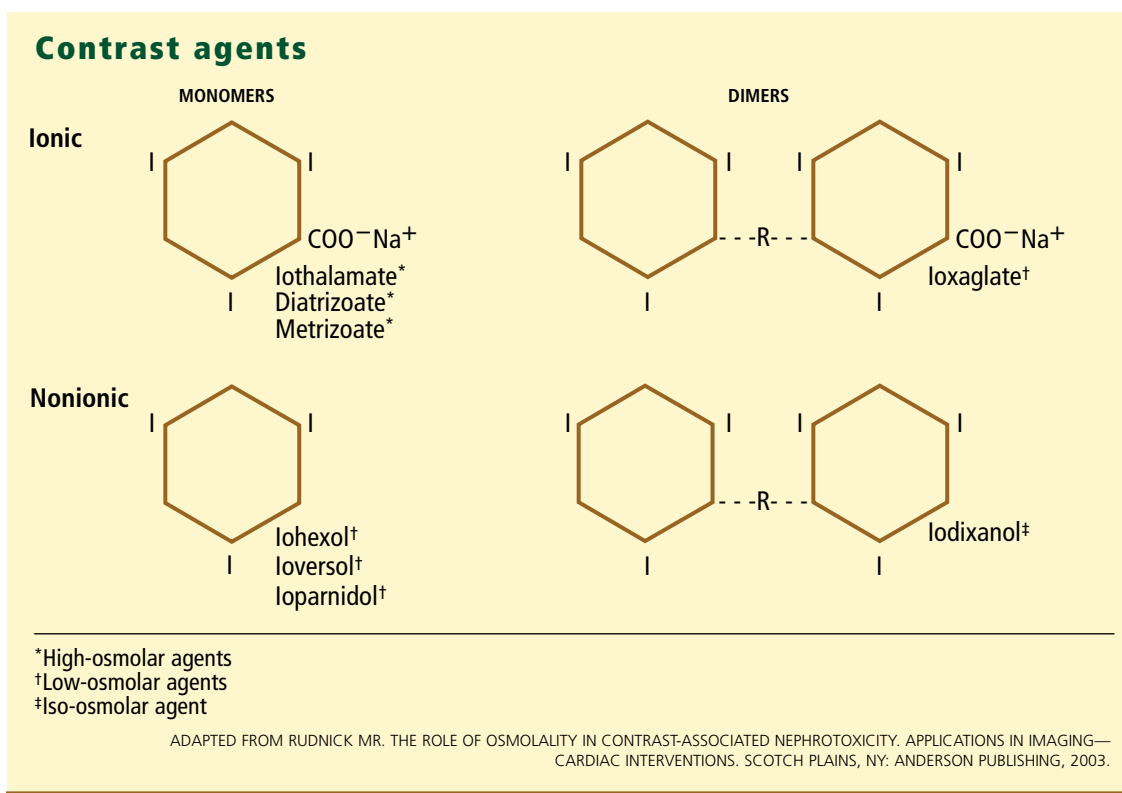
This review examines the multiple dimensions of contrast-induced nephropathy. We will discuss the evidence for using various strategies for prophylaxis—hydration, *N*-acetylcysteine, sodium bicarbonate, theophylline, and hemofiltration—and then give our recommendations.

## ■ STILL COMMON

Contrast-induced nephropathy continues to be a common form of hospital-acquired acute renal failure.<sup>1</sup> Although its incidence is low in patients with normal renal function, it can be much higher in those with severe renal insufficiency at baseline.

\*Dr. Rudnick has indicated that he has received grant or research support from, serves as a consultant for, and is on the speakers' bureau of the GE Healthcare corporation.

†Dr. Goldfarb has indicated that he is on the speakers' bureau of the GE Healthcare corporation.



**FIGURE 1**

Moreover, an enormous number of patients receive contrast agents. For example, in 2000, approximately 1,318,000 diagnostic cardiac catheterizations and 561,000 percutaneous transluminal coronary angioplasty procedures were performed, which are just two of the many procedures in which contrast is used.<sup>2</sup>

**■ TYPES OF CONTRAST MEDIA**

The earliest contrast agents were ionic, containing a sodium atom that dissociated from the molecule in aqueous solution. Each molecule of the agent carried three iodine atoms. Therefore, these agents required two osmotically active particles to deliver three iodine atoms, and they had extremely high osmolalities (about 2,000 mOsm/L). These agents, termed *high-osmolar* or *ionic*, were the predominant ones used until the 1980s (FIGURE 1).

The next generation, introduced in the 1980s and still the predominant contrast media in use, are nonionic.<sup>3</sup> Since they therefore need only one osmotically active particle to deliver three iodine atoms, their osmolality

is only about 600 to 900 mOsm/L, and they are termed *low-osmolar*.

Both types of agents are monomers, with one benzene ring and three iodine atoms. Dimer molecules consisting of two joined benzene rings contain a total of six iodine atoms per molecule. There is one ionic dimer, ioxaglate, which has a 6:2 or 3:1 ratio of iodine atoms to osmotically active particles and has an osmolality of 600 mOsm/L, similar to other low-osmolar contrast agents.

The newest contrast agent, iodixanol, is a nonionic dimer. The chemical structure of this agent allows six iodine atoms to be attached to one osmotically active particle, resulting in an osmolality of 300 mOsm/L, which is iso-osmolar with normal plasma.

**■ DOES CONTRAST NEPHROPATHY INCREASE MORTALITY?**

Patients undergoing percutaneous coronary interventions have a higher mortality rate if nephropathy develops.<sup>4,5</sup> The risk of dying is greatest in patients who require dialytic support because of the nephropathy. For example,

The newest contrast agent is a nonionic dimer and is iso-osmolar



McCullough et al<sup>5</sup> found that in-hospital mortality rates were 1.1% for patients with no contrast-induced nephropathy compared with 7.1% for those with nephropathy alone, and up to 35.7% for those with nephropathy requiring dialysis.

In this and other studies, patients in whom nephropathy developed had a higher prevalence of preexisting conditions and periprocedural complications than those in whom it did not develop.

The comorbidities complicate the analysis, as one cannot determine with certainty whether contrast-induced nephropathy contributes directly to mortality in this population, whether this complication simply selects out a subgroup of patients at significantly greater risk of dying, or if both possibilities are correct. Multivariate regression analyses demonstrated that contrast-induced nephropathy was an independent predictor of death, but this type of analysis does not prove a cause-and-effect relationship.

The question of whether contrast-induced nephropathy directly contributes to mortality is further confounded by recent studies demonstrating an increased risk of death in cardiac patients with preexisting renal insufficiency undergoing coronary revascularization.<sup>6,7</sup> Since most patients who develop contrast-induced nephropathy have preexisting renal insufficiency, the specific contribution of contrast-induced nephropathy alone to increased mortality is unclear.

#### ■ FEW PATIENTS NEED DIALYSIS

In most cases of contrast-induced nephropathy, serum creatinine begins to rise within 24 to 48 hours after exposure, reaches a peak within 3 to 5 days, and then returns to baseline levels within 7 to 10 days.<sup>8</sup> In more severe cases, the creatinine concentration may not peak until 5 to 10 days, and the increase may be associated with oliguria.<sup>8,9</sup>

Fortunately, few patients need acute hemodialysis. Diabetic patients who take insulin and have advanced renal insufficiency are more susceptible to prolonged acute renal failure, often with oliguria or the need for hemodialysis.

Findings on urinalysis in patients with contrast-induced nephropathy are similar to those in patients with other causes of acute tubular necrosis. Typical findings are coarse granular casts, renal tubular epithelial cells, and amorphous debris.

#### ■ RISK FACTORS

**Preexisting renal insufficiency** is the single greatest risk factor.<sup>8,9</sup> In one comprehensive review, an estimated 60% of patients with contrast-induced nephropathy had preexisting renal insufficiency.<sup>9</sup>

The more severe the baseline renal insufficiency, the greater the risk.<sup>8,9</sup> Although the risk of contrast-induced nephropathy for a given serum creatinine value can vary widely, one can roughly estimate the percent risk by multiplying the serum creatinine concentration in milligrams per deciliter by 10.

**Diabetes mellitus** is often cited as a risk factor for contrast-induced nephropathy,<sup>9,10</sup> but the risk ascribed to it is probably due to coexisting renal insufficiency, usually diabetic nephropathy, rather than to the diabetes per se.<sup>9,10</sup> In recent prospective studies, the incidence in patients with diabetes and normal renal function was similar to that in nondiabetic patients with normal renal function.<sup>10,11</sup>

On the other hand, patients with diabetes and preexisting renal insufficiency have a greater risk for contrast-induced nephropathy than nondiabetic patients with similar levels of preexisting renal insufficiency.<sup>10,11</sup> Moreover, when patients in this high-risk group develop nephropathy, they more often develop oliguria and need dialysis.<sup>12</sup> As with patients without diabetes, the risk of contrast-induced nephropathy is directly proportional to the severity of preexisting renal insufficiency.

**Volume of contrast media.** Some studies found a correlation between the volume of contrast given and the risk of nephropathy,<sup>11–13</sup> whereas other studies did not.<sup>14</sup>

Cigarroa et al<sup>13</sup> used a predetermined formula based on body weight and baseline renal function to limit the volume of contrast media in patients undergoing coronary angiography. The limit was 5 mL of contrast per kg of body weight up to a maximum of 300 mL, divided by the serum creatinine concentration in mil-

**To calculate the risk of contrast nephropathy, multiply the creatinine level by 10**

ligrams per deciliter. Nephropathy developed in 21% of the patients in whom the total volume of contrast exceeded the formula amount, compared with 2% ( $P < .001$ ) of patients in whom the contrast volume fell within the prescribed limit.

**Multiple myeloma** has traditionally been considered a risk factor for contrast-induced nephropathy.<sup>9,10</sup> However, McCarthy and Becker<sup>15</sup> reviewed several retrospective studies of contrast use in patients with myeloma and found an incidence of nephropathy of only 0.6% to 1.25%, indicating that this group is not at increased risk with modern contrast agents, provided that volume expansion is achieved at the time of exposure.

Even though multiple myeloma should not be an absolute contraindication for contrast use, clinical prudence warrants performing radiologic studies with contrast only if necessary and avoiding dehydration in these patients.

#### ■ HOW DO CONTRAST AGENTS CAUSE NEPHROPATHY?

The primary pathways by which contrast agents cause nephropathy are by renal ischemia (by reducing blood flow or increasing oxygen demand) and, possibly, by direct toxicity to tubular epithelial cells.

##### **Renal ischemia**

After contrast is injected, renal blood flow transiently increases and then decreases over a longer time, suggesting that renal ischemia is a major factor in the pathogenesis of contrast-induced nephropathy.<sup>16</sup>

In experimental studies of contrast-induced nephropathy, the kidneys show pathologic ischemic changes—necrosis of the medullary thick ascending limbs as well as tubular collapse and casts—primarily in the outer medullary area of the kidney.<sup>17</sup> Moreover, contrast agents cause a marked decrease in medullary oxygenation that can be directly measured with oxygen microelectrodes.<sup>18</sup>

Based on these observations, the following mechanism for acute renal failure induced by contrast agents has been proposed.<sup>19,20</sup>

Even under normal conditions, the renal medulla is poorly oxygenated, making it par-

ticularly susceptible to hypoxic injury. The oxygen tension in the medulla is 10 to 20 mm Hg compared with 50 mm Hg in the cortex. Reasons for the low oxygen tension are countercurrent exchange of oxygen between the vasa recta and oxygen use by active transport of sodium in the ascending limb of the loop of Henle.<sup>19</sup>

Contrast agents reduce the oxygen tension in both the cortex and the medulla.<sup>18</sup> This effect may be due to increased work of active transport in response to an osmotic diuresis from hyperosmolar agents, as well as the release of vasoconstrictive compounds such as endothelin (see below). Furthermore, blockade of vasodilatory compounds such as nitrous oxide and prostaglandins appears to markedly exacerbate contrast-induced medullary hypoxic injury.<sup>19</sup>

##### **Vasoconstriction**

Many substances may mediate renal vasoconstriction and subsequent hypoxic injury. Of note, adrenergic stimulation and activation of the renin-angiotensin system do not seem to be involved in contrast-induced vasoconstriction.<sup>16,17</sup> Prostaglandins with vasodilatory properties may counter the vasoconstriction induced by contrast media, since pretreatment with indomethacin is necessary to induce experimental contrast-induced renal injury.<sup>18</sup>

**Endothelin.** Multiple experimental observations suggest that endothelin, a potent renal vasoconstrictor, may play a critical role in contrast-mediated vasoconstriction.<sup>8</sup>

These observations led to a clinical trial in which patients with chronic kidney disease undergoing cardiac angiography were randomized to receive either the endothelin receptor antagonist SB 290670 or placebo.<sup>21</sup> Surprisingly, the incidence of contrast-induced nephropathy was higher in the treatment group (56%) than in the placebo group (29%;  $P = .002$ ).

**Adenosine.** The role of adenosine in the pathogenesis of contrast-induced nephropathy is described in detail in an excellent review by Pflueger et al.<sup>22</sup> Adenosine causes vasodilation through A<sub>2</sub> stimulation of the efferent arteriole and medullary capillaries, and it also causes vasoconstriction through A<sub>1</sub> stimulation of the afferent arterioles. However, renal vasoconstriction dominates, explaining why

Even under normal conditions, the renal medulla is poorly oxygenated



intrarenal adenosine infusion results in a decrease in renal blood flow.<sup>22</sup>

In experimental studies, theophylline, a nonselective adenosine receptor antagonist, inhibited contrast-media induced renal vasoconstriction.<sup>22</sup>

### Role of osmolality

Several clinical and experimental observations suggest that the hyperosmolality of contrast media may play a role in the pathogenesis of contrast-induced nephropathy. Clinical studies demonstrated that low-osmolar contrast agents cause less nephrotoxicity than high osmolar agents.<sup>11,23</sup> Furthermore, in one study,<sup>24</sup> the incidence of contrast-induced nephropathy was lower with an iso-osmolar contrast agent than with a low-osmolar agent.

In experimental studies, hypertonic solutions of saline or mannitol reduce the glomerular filtration rate and renal blood flow and increase enzymuria similarly to high-osmolar contrast media but with a lesser magnitude.<sup>16,25</sup> A theory to account for these nonspecific adverse effects is that hyperosmolality activates tubuloglomerular feedback or causes an increase in tubular hydrostatic pressures, either of which could lead to a decrease in glomerular filtration. In addition, the osmotic diuresis produced by contrast media may result in increased active transport of sodium in the thick ascending limb and also in vasoconstriction, and both of these could lead to worsened medullary hypoxemia.<sup>18–20</sup>

On the other hand, most studies in animals specifically comparing iso-osmolar contrast agents (iodixanol and iotrolan) with high-osmolar and low-osmolar contrast agents have not demonstrated any lower rate of renal abnormalities with the iso-osmolar agents.<sup>26,27</sup> The reason may be that the iso-osmolar agents are more viscous, which could increase red blood cell aggregation and decrease renal blood flow, offsetting any reduction in medullary hypoxemia from their lower osmolality.

### Reactive oxygen species

Reactive oxygen species formed as a result of postischemic oxidative stress can lead to acute renal failure through their direct effects on renal endothelial cells, which include apop-

totic cell death. Adenosine's role in the pathogenesis of contrast-induced nephropathy may be due to this molecule's ability to increase generation of oxygen-free radicals.<sup>28</sup> The possible benefit of *N*-acetylcysteine and sodium bicarbonate in preventing contrast-induced nephropathy (see below) is hypothesized to be due to the ability of these compounds to mitigate oxidative injury.

### Direct cellular toxicity

A number of experimental observations suggest that contrast agents are directly toxic to kidney cells, causing proximal cell vacuolization, interstitial inflammation, cellular necrosis, and enzymuria.<sup>8,17</sup> Furthermore, suspensions of proximal tubular segments exposed to contrast media showed abnormalities in several markers of cellular injury, that were potentiated by hypoxia and were more pronounced with high-osmolar agents than with low-osmolar agents.<sup>29</sup>

### ■ PREVENTIVE MEASURES: MANY TRIED, FEW SUCCEEDED

Currently, there is no treatment to reverse or ameliorate contrast-induced nephropathy once it occurs, but prophylaxis is possible.

Many preventive measures have been tried that may interfere with one or more of the currently accepted pathogenetic mechanisms for contrast-induced nephropathy (TABLE 1). However, many of these measures later failed to show benefits in well-designed, prospective, randomized, double-blinded trials. Among this group are diuretics,<sup>30</sup> mannitol,<sup>30</sup> dopamine,<sup>31</sup> atrial natriuretic peptide,<sup>32</sup> endothelin receptor antagonists,<sup>21</sup> and fenoldopam.<sup>33</sup>

This review will focus only on the strategies that have possible or proven prophylactic value.

### Hydration is indicated, but what kind, how much?

Hydration is the primary intervention for preventing contrast nephropathy.<sup>34</sup>

The theoretical rationale for hydration is that it should decrease the activity of the renin-angiotensin system, reduce the levels of other vasoconstrictive hormones such as

**More contrast nephropathy occurred with saline plus mannitol or furosemide than with saline alone**



TABLE 1

**Strategies for preventing contrast-induced nephropathy**

**Strategies that do not work**

- Mannitol
- Furosemide
- Dopamine
- Atrial natriuretic factor
- Fenoldopam
- Hemodialysis

**Strategies that may work**

- Calcium channel blockers
- Theophylline
- Iso-osmolar contrast media
- N*-acetylcysteine
- Hemofiltration
- Sodium bicarbonate
- Ascorbic acid
- Prostaglandins

**Currently recommended strategies**

- Employ noniodinated contrast studies
- Avoid nonsteroidal anti-inflammatory drugs
- Provide adequate time between contrast procedures
- Minimize contrast volume
- Parenteral hydration
- Low-osmolar or iso-osmolar contrast media

endothelin, increase sodium diuresis, decrease tubuloglomerular feedback, prevent tubular obstruction, protect against reactive oxygen species, and dilute the contrast media in the tubule, thus decreasing any direct nephrotoxic effect of the contrast agent on the tubular epithelium.<sup>34</sup>

Several studies in animals demonstrated hydration with saline infusions to be beneficial in preventing contrast-induced nephropathy.<sup>35</sup>

Early clinical studies used historical controls for comparison and also suggested that hydration is beneficial. Subsequently, intravenous hydration became the standard method to prevent contrast-induced nephropathy.<sup>8,9</sup>

There have been a few prospective randomized studies comparing saline alone vs other therapies as prophylactic strategies.<sup>21,30-33</sup>

Solomon et al<sup>30</sup> randomized patients with chronic kidney disease undergoing cardiac angiography to receive either saline alone,

saline and mannitol, or saline and furosemide. All three groups received 0.45% saline intravenously at 1 mL/kg/hour for 12 hours before and 12 hours after receiving contrast. Nephropathy occurred in 11% of patients receiving saline alone vs 28% who received saline and mannitol and 40% who received saline and furosemide.

Different regimens of saline hydration have been used, but no one regimen has demonstrated clear superiority.

Trivedi et al<sup>36</sup> prospectively randomized patients undergoing cardiac angiography to receive either intravenous saline for 12 hours both before and after catheterization or oral fluids only, taken as desired. Contrast-induced nephropathy occurred in 3.7% of those who received intravenous saline vs 34.6% of those who received only oral fluids.

In contrast, the Preparation for Angiography in Renal Dysfunction (PREPARED) trial<sup>37</sup> showed that, in patients with chronic kidney disease undergoing coronary angiography, hydration on an outpatient basis before catheterization, coupled with a brief period of intravenous hydration, was equivalent to overnight intravenous hydration.

Bader et al<sup>38</sup> randomized patients undergoing computed tomography or digital angiography to receive either 2,000 mL of intravenous fluid over 24 hours (12 hours before and 12 hours after contrast) or 300 mL of intravenous fluid during the radiologic procedure. The glomerular filtration rate fell by 18.3 mL/minute in the continuous infusion group compared with a 34.6 mL/minute fall in the bolus infusion group ( $P < .05$ ), suggesting that slow hydration is superior to bolus expansion during the procedure.

The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) study<sup>39</sup> tested the hypothesis that forced diuresis with maintenance of intravascular volume would result in less contrast-induced renal injury. Although no difference in the incidence of contrast-induced nephropathy was observed between patients who underwent forced diuresis and those who did not, the incidence in participants with urine flow rates greater than 150 mL/hour was 21.6% vs 45.9% in those with lower urine flow rates ( $P = .03$ ).



Mueller et al<sup>40</sup> compared the use of isotonic (0.9%) saline (n = 685) vs half-isotonic (0.45%) saline (n = 698) in patients undergoing coronary angioplasty. Both groups received about 2,000 mL of intravenous fluid. The incidence of contrast-induced nephropathy was significantly lower with isotonic saline (0.7%) than with half-isotonic saline (2%,  $P = .04$ ).

**Comment.** These experimental and clinical studies support the use of intravenous hydration to prevent contrast-induced nephropathy, especially in patients with azotemia at high risk. As yet, no sufficiently powered, controlled, prospective trials have examined the minimally effective length of time, optimal rate, and fluid composition of intravenous hydration required before and after contrast administration in high-risk azotemic patients.

### ***N*-acetylcysteine: Data are conflicting**

*N*-acetylcysteine has been shown in experiments in animals to ameliorate renal injuries from ischemia and nephrotoxins.<sup>41</sup> Potential mechanisms include antioxidation (either directly as a free radical oxygen scavenger or indirectly through glutathione production),<sup>41</sup> preventing apoptotic cell death mediated by the generation of oxygen free radicals, and vasodilation.<sup>42</sup>

Tepel et al<sup>43</sup> first found *N*-acetylcysteine beneficial in a study of 83 patients with chronic renal failure (32.5% had diabetic nephropathy) undergoing computed tomography with contrast. Patients received intravenous saline for 12 hours before and after receiving the contrast and were prospectively randomized to receive either *N*-acetylcysteine 600 mg by mouth twice daily 1 day before and on the day of the study (total of four doses over 2 days) or placebo. Contrast-induced nephropathy occurred in 2% of the *N*-acetylcysteine group vs 21% of the placebo group ( $P = .01$ ; relative risk 0.1).

Several subsequent studies confirmed the value of *N*-acetylcysteine in preventing contrast-induced nephropathy, all in patients undergoing cardiac angiography.<sup>41</sup> Based on these data, *N*-acetylcysteine became widely accepted as a prophylactic therapy.

Because *N*-acetylcysteine undergoes sig-

nificant first-pass metabolism and its oral administration poses logistical problems, Baker et al<sup>44</sup> evaluated its intravenous use. acetylcysteine was given intravenously at a dose of 150 mg/kg in 500 mL of normal saline solution over 30 minutes immediately before contrast exposure and then 50 mg/kg in 500 mL of normal saline solution over the next 4 hours. Contrast-induced nephropathy occurred in 5% of the *N*-acetylcysteine group compared with 21% of the saline-alone group (relative risk 0.28,  $P = .045$ ). These results suggest that prolonged use of *N*-acetylcysteine before contrast exposure may not be necessary.

On the other hand, many other studies did not demonstrate a prophylactic value for *N*-acetylcysteine.<sup>41</sup> For example, Durham et al<sup>45</sup> studied 79 patients with chronic kidney disease who underwent diagnostic cardiac catheterization, percutaneous coronary intervention, or both. The patients were randomly assigned to receive oral acetylcysteine or placebo. All patients received hydration with 0.45% saline for up to 12 hours before and after catheterization. There was no significant difference in the incidence of contrast-induced nephropathy between the two groups: 26.3% in the acetylcysteine group and 22% in the control group.

Nallamothu et al<sup>46</sup> performed a meta-analysis of 20 studies involving 2,195 patients and calculated that the relative risk of contrast nephropathy in patients who received *N*-acetylcysteine was 0.73 (95% confidence interval 0.52–1.0;  $P = .08$ ). Pannu et al<sup>47</sup> performed another meta-analysis of 15 studies involving 1,776 patients and calculated the relative risk at 0.65 (95% confidence interval 0.43–1.00). Both groups of investigators were cautious in their conclusions, pointing out that the individual studies showed substantial heterogeneity in design and results and calling for definitive studies. Some of the variables that differed among the studies published to date include the severity of baseline renal insufficiency, the percentage of diabetic patients, the type and amount of contrast used, the amount and timing of *N*-acetylcysteine administration, and the amount of hydration.

**Conclusions.** Although *N*-acetylcysteine is safe, easy to use, and inexpensive, its value

**Studies of  
*N*-acetylcysteine differed  
in design and  
results**

in preventing contrast-induced nephropathy remains controversial.

### **Theophylline:**

#### **Not recommended at this time**

Several reports suggest that theophylline, an adenosine antagonist, prevents contrast-induced nephropathy.<sup>22,48</sup>

Erley et al<sup>48</sup> randomized 39 patients who received contrast media to receive either intravenous theophylline or placebo. Although no patient in either group developed contrast-induced nephropathy, the glomerular filtration rate decreased in the placebo group from 88 mL/minute at baseline to 75 mL/minute 4 hours after contrast administration; it remained unchanged in the theophylline group.

In several other placebo-controlled studies, theophylline (given orally or intravenously) prevented contrast-induced falls in creatinine clearance, but all the studies were in low-risk patients, and contrast-induced nephropathy was not seen in any groups.

Theophylline has potential risks, including ventricular arrhythmias, seizures, and shock—all of which may be potentiated by a variety of other drugs.<sup>22</sup>

**Conclusions.** The data regarding theophylline are mixed. Favorable studies were limited by small numbers, absence of high-risk patients, and a failure to demonstrate differences in the incidence of contrast-induced nephropathy. Therefore, theophylline cannot be recommended as standard prophylaxis against contrast-induced nephropathy at this time.

#### **Low-osmolar agents are better than high osmolar agents**

Introduced in the 1980s, nonionic low-osmolar contrast agents have replaced ionic high-osmolar agents as the standard intravascular contrast media because of their lower incidence of adverse effects.<sup>3</sup>

Studies in animals have demonstrated that, compared with high-osmolar agents, low-osmolar agents result in less nephrotoxicity but still can cause nephropathy.<sup>8</sup> Initial clinical studies comparing high-osmolar vs low-osmolar contrast agents failed to demonstrate a difference between these two types of agents but were underpowered in respect to

high-risk azotemic patients.<sup>8</sup>

In 1995, Rudnick et al<sup>11</sup> performed a prospective, randomized, double-blind study comparing the high-osmolar contrast agent diatrizoate with the low-osmolar contrast agent iohexol in 1,196 patients, including 509 azotemic patients, of whom 213 had diabetes. In patients without azotemia, the incidence of contrast-induced nephropathy was negligible with either agent, regardless of whether or not the patient had diabetes. However, in patients with azotemia but without diabetes, the incidence of contrast-induced nephropathy was 7% with the high-osmolar agent vs 4% with the low-osmolar agent. In patients with azotemia and diabetes, the differences were even more pronounced: 27% with the high-osmolar agent and 12% with the low-osmolar agent.

A subsequent meta-analysis indicated that low-osmolar agents reduced the incidence of contrast-induced nephropathy by 50%.<sup>23</sup>

#### **Are iso-osmolar agents better than low-osmolar agents?**

The iso-osmolar contrast agents have undergone experimental and clinical studies comparing their nephrotoxicity with that of the currently popular low-osmolar agents. As discussed above, these third-generation agents have not demonstrated less nephrotoxicity than low-osmolar agents in studies in animals. Furthermore, only a few clinical studies have compared the incidence of contrast-induced nephropathy with the two types of agents.<sup>24,49</sup>

Aspelin et al<sup>24</sup> performed a prospective, randomized, double-blind, multicenter trial in 129 patients with azotemia and diabetes. Patients were randomly assigned to receive either iohexol (a low-osmolar agent) or iodixanol (an iso-osmolar agent). The incidence of contrast-induced nephropathy was 3% with the iso-osmolar agent vs 26% with the low-osmolar agent (odds ratio 0.09,  $P = .002$ ).

Larger randomized trials will be needed to verify these encouraging results, especially with comparisons to other low-osmolar contrast agents.

#### **Hemodialysis and hemofiltration**

Numerous studies have demonstrated that 2 to 3 hours of hemodialysis effectively removes 60% to 90% of contrast medium.<sup>50</sup> Several

**Low-osmolar agents have become the standard**





studies explored the prophylactic value of hemodialysis in high-risk patients, but most failed to demonstrate a reduced incidence of contrast-induced nephropathy.<sup>50</sup>

On the other hand, Marenzi et al<sup>51</sup> recently found that hemofiltration significantly reduced contrast-induced nephropathy in patients at high risk. In this study, patients with chronic kidney disease undergoing coronary angiography were randomized to undergo either hemofiltration in an intensive care unit or parenteral saline hydration. Hemofiltration was started 4 to 6 hours before contrast administration, stopped for coronary angiography, then resumed for an additional 18 to 24 hours. Isotonic saline was used as replacement fluid and was given at a rate of 1 L per hour, which matched the ultrafiltration rate so that no net fluid loss resulted. In the control group, isotonic saline was given at 1 mL/kg/hour for 6 to 8 hours before and 24 hours after angiography.

The incidence of contrast-induced nephropathy was 5% in the hemofiltration group compared with 50% in the control group ( $P < .001$ ). The in-hospital mortality rate was 2% in the hemofiltration group compared with 14% in the control group ( $P = .02$ ).

Despite these impressive results, the conclusions of this study should be viewed with some caution. Removal of creatinine by hemofiltration per se could result in a lower incidence of contrast-induced nephropathy, although this alone would not account for differences in mortality. Moreover, the mortality rate in the control group was inordinately high, suggesting that it was not a good representative cohort. Both groups received an extraordinary volume of contrast (approximately 250 mL) for patients with moderately severe chronic kidney disease (their baseline mean creatinine concentration was 3.0 mg/dL).

**Conclusions.** Given these reservations, due to the logistical effort and high cost associated with hemofiltration, larger randomized trials should be performed before this technique can be recommended as standard prophylaxis against contrast-induced nephropathy in high-risk patients.

Somewhat related is the not-infrequent clinical question of when to perform the next hemodialysis treatment in a patient undergoing chronic hemodialysis who receives

intravascular contrast media. Although this question has not been extensively investigated in clinical trials, there is evidence that most patients can safely wait 24 to 36 hours after contrast exposure until their next hemodialysis treatment.

#### **Sodium bicarbonate: Data are preliminary**

Merten et al,<sup>52</sup> in a randomized controlled trial at a single center, compared hydration with sodium bicarbonate vs sodium chloride to prevent contrast-induced nephropathy in azotemic patients receiving low-osmolar contrast agents. Both infusions contained 154 mEq of either sodium chloride or sodium bicarbonate in 1 L of 5% dextrose and water. A close approximation of the sodium bicarbonate solution can be achieved by adding 3 ampules (150 mEq) of sodium bicarbonate to 1 L of 5% dextrose in water: the final sodium bicarbonate concentration is 130 mEq/L. The infusion rate for either fluid was 3 mL/kg/hour for 1 hour before contrast administration, followed by 1 mL/kg/hour during contrast administration and then for 6 hours afterward.

Contrast-induced nephropathy occurred in 1.7% of patients who received sodium bicarbonate compared with 13.6% of patients who received sodium chloride ( $P = .02$ ).

The benefit of sodium bicarbonate in preventing contrast-induced nephropathy is probably not simply due to volume expansion, which was similar between treatment groups. The authors postulate instead that sodium bicarbonate may reduce the formation of oxygen free radicals (a pH-dependent reaction), previously reported to play a pathogenetic role in contrast-induced nephropathy.<sup>52</sup>

**Conclusions.** We agree with the authors that sodium bicarbonate infusion may provide a simple, safe, and inexpensive method to prevent contrast-induced nephropathy but the results of this study need to be confirmed in a larger, multicenter, prospective randomized trial.

#### **■ CURRENT RECOMMENDATIONS**

The use of intravascular contrast in patients at risk for contrast-induced nephropathy should be considered only when alternative imaging tests that do not use iodinated contrast cannot pro-

**Start saline hydration 2–4 hours before the procedure and continue 4–6 hours after**

vide the necessary clinical information. In many cases, ultrasonography, nuclear medicine, magnetic resonance, and unenhanced computed tomography can provide sufficient data without exposing the patient to iodinated contrast media and the risk of contrast-induced nephropathy.

When exposure to iodinated contrast media is unavoidable, we recommend the following approach.

- Nonsteroidal anti-inflammatory drugs should be discontinued before contrast exposure.
- Patients should receive hydration with intravenous normal saline starting 2 to 4 hours before receiving the contrast, during the radiographic procedure, and continuing 4 to 6 hours afterward. The duration of the saline infusion should be longer with more severe chronic kid-

ney disease or if underlying diabetic nephropathy is present.

- The radiologist or cardiologist should use the smallest volume of contrast needed to obtain the critical imaging.
- Based on currently available data, there may be an advantage in using iso-osmolar contrast media.
- Hypotension in the peri-imaging period should be avoided if possible.
- *N*-acetylcysteine and bicarbonate hydration can be used since they are safe and inexpensive, although their use is somewhat controversial.
- Serum creatinine should be measured approximately 48 hours after contrast exposure to determine if contrast-induced nephropathy has occurred.

■ REFERENCES

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; 74:243–248.
2. American Heart Association. Heart Disease and Stroke Statistics—2003 Update, pp 38–39.
3. McClennan BL. Low-osmolality contrast media: premises and promises. *Radiology* 1987; 162:1–8.
4. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *JAMA* 1996; 275:1489–1494.
5. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997; 103:368–375.
6. Szczech LA, Reddan DN, Owen WF Jr, et al. Differential survival after coronary revascularization procedures among patients with renal insufficiency. *Kidney Int* 2001; 60:292–299.
7. Reinecke H, Trey T, Matzkies F, Fobker M, Breithardt G, Schaefer RM. Grade of chronic renal failure, and acute and long-term outcome after percutaneous coronary interventions. *Kidney Int* 2003; 63:696–701.
8. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Contrast media-associated nephrotoxicity. *Semin Nephrol* 1997; 17:15–26.
9. Berns AS. Nephrotoxicity of contrast media. *Kidney Int* 1989; 36:730–740.
10. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism—a critical review. *Am J Kidney Dis* 1994; 24:713–727.
11. Rudnick MR, Goldfarb S, Wexler L, et al. The Iohexol Cooperative Study. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. *Kidney Int* 1995; 47:254–261.
12. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med* 1990; 89:615–620.
13. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 1989; 86(6 Pt 1):649–652.
14. Barrett BJ, Parfrey PS, Vavasour HM, et al. Contrast nephropathy in patients with impaired renal function: high versus low osmolar media. *Kidney Int* 1992; 41:1274–1279.
15. McCarthy CS, Becker JA. Multiple myeloma and contrast media. *Radiology* 1992; 183:519–522.
16. Katzberg RW, Morris TW, Burgener FA, Kamm DE, Fischer HW. Renal renin and hemodynamic responses to selective renal artery catheterization and angiography. *Invest Radiol* 1977; 12:381–388.
17. Heyman SN, Brezis M, Reubinoff CA, et al. Acute renal failure with selective medullary injury in the rat. *J Clin Invest* 1988; 82:401–412.
18. Heyman SN, Brezis M, Epstein FH, Spokes K, Silva P, Rosen S. Early renal medullary hypoxic injury from radiocontrast and indomethacin. *Kidney Int* 1991; 40:632–642.
19. Heyman SN, Rosen S, Brezis M. Radiocontrast nephropathy: a paradigm for the synergism between toxic and hypoxic insults in the kidney. *Exp Nephrol* 1994; 2:153–157.
20. Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. *N Engl J Med* 1995; 332:647–655.
21. Wang A, Holcslaw T, Bashore TM, et al. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. *Kidney Int* 2000; 57:1675–1680.
22. Pflueger A, Larson TS, Nath KA, King BF, Gross JM, Knox FG. Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. *Mayo Clin Proc* 2000; 75:1275–1283.
23. Barrett BJ, Carlisle EJ. Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology* 1993; 188:171–178.
24. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ; Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003; 348:491–499.
25. Talner LB, Rushmer HN, Coel MN. The effect of renal artery injection of contrast material on urinary enzyme excretion. *Invest Radiol* 1972; 7:311–322.
26. Liss P, Nygren A, Erikson U, Ulfendahl HR. Injection of low and iso-osmolar contrast medium decreases oxygen tension in the renal medulla. *Kidney Int* 1998; 53:698–702.
27. Lancelot E, Idee JM, Laclede C, Santus R, Corot C. Effects of two dimeric iodinated contrast media on renal medullary blood perfusion and oxygenation in dogs. *Invest Radiol* 2002; 37:368–375.
28. Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC Jr. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. *Am J Physiol* 1990; 258(1 Pt 2):F111–F120.
29. Messana JM, Cieslinski DA, Nguyen VD, Humes HD. Comparison of the toxicity of the radiocontrast agents, iopamidol and diatrizoate, to rabbit renal proximal tubule cells in vitro. *J Pharmacol Exp Ther* 1988; 244:1139–1144.



30. **Solomon R, Werner C, Mann D, D'Elia J, Silva P.** Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994; 331:1416–1420.
31. **Weisberg LS, Kurnik PB, Kurnik BR.** Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int* 1994; 45:259–265.
32. **Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS.** Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998; 31:674–680.
33. **Stone GW, McCullough PA, Tumlin JA, et al, for the CONTRAST Investigators.** Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; 290:2284–2291.
34. **Erley CM.** Does hydration prevent radiocontrast-induced acute renal failure? *Nephrol Dial Transplant* 1999; 14:1064–1066.
35. **Vari RC, Natarajan LA, Whitescarver SA, Jackson BA, Ott CE.** Induction, prevention and mechanisms of contrast media-induced acute renal failure. *Kidney Int* 1988; 33:699–707.
36. **Trivedi HS, Moore H, Nasr H, et al.** A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract* 2003; 93:C29–C34.
37. **Taylor AJ, Hotchkiss D, Morse RW, McCabe J.** PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest* 1998; 114:1570–1574.
38. **Bader BD, Berger ED, Heede MB, et al.** What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? *Clin Nephrol* 2004; 62:1–7.
39. **Stevens MA, McCullough PA, Tobin KJ, et al.** A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol* 1999; 33:403–411.
40. **Mueller C, Buerkle G, Buettner HJ, et al.** Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1,620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002; 162:329–336.
41. **Fishbane S, Durham JH, Marzo K, Rudnick M.** *N*-Acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol* 2004; 15:251–260.
42. **Heyman SN, Goldfarb M, Shina A, Karmeli F, Rosen S.** *N*-Acetylcysteine ameliorates renal microcirculation: studies in rats. *Kidney Int* 2003; 63:634–641.
43. **Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W.** Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000; 343:180–184.
44. **Baker CS, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ.** A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. *J Am Coll Cardiol* 2003; 41:2114–2118.
45. **Durham JD, Caputo C, Dokko J, et al.** A randomized controlled trial of acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int* 2002; 62:2202–2207.
46. **Nallamothu BK, Shojania KG, Saint S, et al.** Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 2004; 117:938–947.
47. **Pannu N, Manns B, Lee H, Tonelli M.** Systematic review of the impact of acetylcysteine on contrast nephropathy. *Kidney Int* 2004; 65:1366–1374.
48. **Erley CM, Duda SH, Schlepckow S, et al.** Adenosine antagonist theophylline prevents the reduction of glomerular filtration after contrast media application. *Kidney Int* 1994; 45:1425–1431.
49. **Chalmers N, Jackson RW.** Comparison of iodixanol and iohexol in renal impairment. *Br J Radiol* 1999; 72:701–703.
50. **Sterner G, Frennby B, Kurkus K, Nyman U.** Does post-angiographic hemodialysis reduce the risk of contrast medium nephropathy? *Scand J Urol Nephrol* 2000; 34:323–326.
51. **Marenzi G, Marana I, Lauri G, et al.** The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; 349:1333–1340.
52. **Merten GJ, Burgess WP, Gray LV, et al.** Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004; 291:2328–2334.

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**ADDRESS:** Michael Rudnick, MD, Presbyterian Medical Center, Medical Office Bldg., Suite 240, 39th and Market Streets, Philadelphia, PA 19104; e-mail rudnick@uphs.upenn.edu.