Contrast-induced nephropathy is an iatrogenic disease caused by the administration of iodinated contrast material to certain at-risk patients. The clinical features include renal failure, with oliguria, anuria, and electrolyte derangements. Contrast-induced nephropathy can prolong hospitalization, result in greater morbidity and mortality, and increase patients’ costs. A variety of preventive and treatment strategies exist, including use of alternative imaging. Critical care nurses need to understand the nephropathy and the patients at risk and to develop a familiarity with prevention, treatment, and outcome. (Critical Care Nurse. 2012;32[6]:15-24)

### Background

CIN is a disorder characterized by the onset of acute renal failure within 24 to 72 hours after the administration of iodinated contrast medium. CIN is generally self-limiting and is
typically asymptomatic, although a few patients experience renal dysfunction and may require dialysis. Despite its typically mild manifestations, CIN is associated with increases in hospital stays, in-hospital mortality, and 1-year mortality. Lengths of stay can be twice as long as the stays of patients without CIN, and both inpatient and 30-day mortality can be as much as 10-fold greater. Several populations of patients are at risk, including patients with preexisting renal disease, congestive heart failure, and diabetes mellitus. Several treatment regimens are available to protect the kidneys during administration of contrast material.

**Contrast Media**

Contrast media are used in a wide array of medical imaging, including CT, magnetic resonance imaging, angiography, and related studies, to enhance visualization of a variety of anatomical structures. Contrast media can be administered intravenously, intra-arterially, rectally, orally, and by inhalation. Of primary interest are contrast media administered via a vascular route, because these agents are the ones most often implicated in CIN. Most intravenous contrast agents are administered by radiology technicians or radiologists, but critical care nurses should know some of the basics of the pharmacology of these agents and some of the complications that occur after administration to understand the risk factors, clinical manifestations, and potential treatments of CIN.

**Characteristics**

Most intravascular contrast agents contain the element iodine. Iodine is a naturally occurring isotope and, because of its large elemental weight, is relatively radiopaque. The radiopacity of a given substance is related to the inability of electromagnetic radiation to travel through the substance. The chemical makeup of iodine allows it to absorb electromagnetic radiation, making the chemical visible on images obtained with several radiological methods. The percentage of iodine in a given contrast agent is related to the efficacy of the agent in enhancing the anatomical structure of interest. Iodine content and the structure and types of bonds that make up the contrast medium also contribute to the osmolality (osmoles of solute per kilogram of solution) of the contrast agent. The osmolality of blood is usually 275 to 299 mOsm/kg.

Pharmacological agents with an osmolality higher than that of blood are considered hyperosmolar and can cause shifts of both solute and water in a variety of organs, particularly the kidneys. The optimal contrast agent retains adequate radiopaque characteristics, has limited reactivity, and is as close to iso-osmolality as possible.

A variety of contrast agents are available for radiological studies. These agents are classified as ionic or nonionic; monomeric or dimeric; and hyperosmolar, hypo-osmolar, or iso-osmolar. Ionic contrast agents contain charged molecules, whereas nonionic agents do not; this characteristic can affect both the reactivity and the osmolality of a contrast agent. Both ionic and nonionic contrast agents are available in monomeric (a single molecule) or dimeric (2 molecules linked together) compounds; this characteristic also affects the osmolality and physical characteristics of a contrast agent. Ionic compounds typically have a higher osmolality than do nonionic compounds and are associated with more contrast-related reactions. Similarly, monomeric agents generally have higher osmolality than do dimeric agents. Osmolality is thought to be linked to the incidence of adverse reactions to contrast media, and thus lower osmolality agents that preserve the radiopaque characteristics of the agents are thought to be advantageous. Consequently, approximately 90% of intravascular contrast agents used today are nonionic and monomeric or dimeric.

**Adverse Reactions**

Allergic reactions to intravascular contrast agents are rare. The incidence is about 5% to 13% for iodinated agents and less than 1% for noniodinated agents. Allergic reactions to contrast material can range from mild discomfort with urticaria to severe, life-threatening...
anaphylactoid reactions manifested by hypotension, hypoxia, and multisystem organ failure. Hypersensitivity to contrast material is often related to the rate of infusion and is generally mild. Hypersensitivity reactions can occur immediately after injection of the contrast agent or may be delayed for a week or more, and the reactions include urticaria, angioedema, bronchospasm, and hypotension. Chemotoxic reactions to contrast media are related to several factors, including the pharmacology of the contrast agent, the dose, and the rate of infusion. Chemotoxic reactions include vasovagal signs and symptoms, arrhythmias, seizures, and end-organ damage (eg, contrast nephropathy).

The pathophysiology and management of allergic reactions to contrast agents are similar to those of other allergic responses. Treatment includes supportive care and administration of steroids and antihistamines. Contrary to popular belief among both patients and practitioners, no evidence supports a link between an allergy to seafood and an allergy to intravenous contrast material. Thus, seafood allergy is not a contraindication to the use of contrast material.

Extravasation of contrast agents, another adverse event, occurs when contrast material leaks out of the intended compartment such as a blood vessel or solid organ. Intravenous administration of contrast material, particularly rapid-bolus autoinjection used for studies of the pulmonary and cardiovascular system, can be associated with marked extravasation. Management of extravasation should include an evaluation of the affected extremity for perfusion and pain. The extremity should be elevated, and most sources recommend application of heat to promote vasodilatation and resorption of the contrast material. In rare instances, such as development of compartment syndrome, surgery may be required to decompress the extravasation.

The rare metal gadolinium is also used in imaging, mostly as a contrast agent in magnetic resonance imaging. Gadolinium is not an iodinated compound, and its use is associated with a low risk for nephropathy. Some reports, however, indicate that use of gadolinium may result in self-limiting acute renal failure or nephrogenic systemic fibrosis, a rare abnormality that involves fibrosis of a variety of organ systems. Patients with preexisting renal failure are the most at-risk patients for nephrogenic systemic fibrosis when gadolinium is used.

Another adverse reaction of contrast agents that affects the kidneys is CIN. The overall incidence of CIN is approximately 12% and can be as high as 50% in at-risk patients with multiple comorbid conditions. For patients who have renal injury due to contrast material, in-hospital mortality is 7% to 35% and 1-year mortality is 12% to 54%.

### Table 1 Risk factors for contrast-induced nephropathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Chronic renal insufficiency (serum creatinine level &gt;1.5 mg/dL)</td>
</tr>
<tr>
<td>Chronic renal insufficiency (serum creatinine level &gt;1.5 mg/dL)</td>
<td>Medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Large-volume studies (&gt;70 mL): angiography, cardiac catheterization</td>
<td></td>
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</tbody>
</table>

To convert to micromoles per liter, multiply by 88.4.

### Contrast-Induced Nephropathy

CIN has no specific, internationally accepted definition, but broadly the condition can be defined as an increase in the serum concentration of creatinine greater than 0.5 mg/dL or a 25% increase in the creatinine level from baseline during the period of 12 to 48 hours after the administration of radiocontrast media.

CIN was first reported in 1954 by Bartels et al, who described the onset of renal failure in a patient with multiple myeloma who was given contrast material for a pyelogram. Since then, thousands of cases of CIN and multiple studies on the nephropathy have been reported. Newer low-osmolality contrast agents have reduced the incidence of CIN but have not entirely eliminated the occurrence. The incidence of CIN varies from 1% to 20%, depending on the definition used.

### Risk Factors

Several groups of patients are at an increased risk for CIN (Table 1). Patients who have normal renal function have almost no risk for renal failure after the administration of contrast material, and evidence of renal failure in these patients suggests another cause for the failure.
An elevation in serum level of creatinine in patients with normal renal function can suggest other causes of prerenal azotemia, including shock and renal tubular acidosis. Other groups of patients, however, are at an increased risk, and identifying these patients is important so that appropriate preventive interventions can be started.

Patients with preexisting renal disease are at increased risk for CIN, and renal failure may be a contraindication for use of contrast material.35,36 A serum creatinine level of 1.5 mg/dL and/or a GFR less than 60 mL/min per 1.73 m² are risk factors for CIN.31,32 Most institutions have an established creatinine level cutoff for the administration of intravascular contrast material, and other imaging techniques may be required for patients whose creatinine level is higher than the cutoff level. Other at-risk groups include patients with diabetes mellitus with renal insufficiency, patients with advanced heart failure, and patients with multiple myeloma.31,33,34 Procedurally, a larger volume of contrast material is used in coronary angiography than in other imaging studies, and patients who have coronary angiography often have one or more comorbid conditions associated with CIN. Consequently, rates of CIN are higher in patients who have this cardiac study than in other patients.35,36

Some evidence suggests that CIN may be dose dependent. Several studies38,39 have indicated that lower volumes of contrast material, less than 70 mL, are associated with lower rates of CIN than are higher volumes, although conflicting reports37 have also been published. One study37 revealed that volumes as low as 20 mL can be associated with CIN in patients with diabetic nephropathy. Whether or not the volume of contrast material used is a risk factor for CIN remains unclear.32,33 Higher osmolality is also associated with an increased risk for CIN, especially in patients whose fluid volume is already decreased or who have a low-flow state such as heart failure or shock. Even the newer, low-osmolality agents are associated with CIN, although the number of annual cases appears to be lower than the number when high-osmolality agents were the predominant imaging agent.14,19

Several medications have been associated with an increased risk for CIN. Recent data14 suggest that the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk for CIN. Toprak34 determined that patients with blockade of the renin-angiotensin cascade had significantly higher incidences of CIN than did control patients. Nonsteroidal anti-inflammatory drugs as a class are associated with renal vasoconstriction and may also increase the risk for CIN.34

**Etiology**

Understanding of the pathophysiology of CIN requires a basic understanding of contrast media. Because of their low lipid solubility, limited interaction with body fluids and cells, low osmolality, and short half-lives of 1 to 2 hours, most contrast agents belong to a class of extracellular tracers.11,13 Contrast agents are designed to enhance visualization of structures without absorption and without alteration of biochemical function. Nevertheless, iodinated contrast media do have some pharmacological effects because of their class-effect osmolality and thus tend to increase plasma volume, decrease blood flow, and decrease the GFR. Most iodinated contrast media have negligible protein binding, so the serum and filtrate concentration of the contrast agent used is equal.14 As a result, contrast media are not reabsorbed by the renal tubule, and thus the reabsorption of water is also diminished. This decrease in the reabsorption of water in turn reduces the GFR. Whether or not this mechanism is responsible for the induction of CIN is not yet known.

Several mechanisms for CIN have been proposed, including renal ischemia, direct cellular injury, production of free radicals, and some combination effect. The exact mechanism has not been established, although both animal and human models of CIN have been created. Several major theories are generally accepted, including renal vasoconstriction of various causes and direct cytotoxic effects of the contrast agent itself.

Ischemia as a mechanism of CIN has been studied in both animal and human models. Some data from animal models suggest that renal vasoconstriction is a component of CIN.19 Evidence from human models indicates that renal blood flow may be decreased to 30% to 45% less than baseline flow for several hours after administration of contrast material.14,20 The proposed mechanisms include vasoconstriction with resultant medullary hypoxia that may be mediated by nitric oxide and prostanoids involved in vasodilatation and activities of free-radical scavengers. In addition, the viscosity within the medullary vascular bed may increase, contributing to medullary hypoxia and resultant

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**Critical Care Nurse** Vol 32, No. 6, DECEMBER 2012 www.ccnonline.org
renal injury. The vasa recta make up the vascular bed of the medulla and require maintenance of a low viscosity because of the small diameter and architecture of the vasculature. In addition, this system has low oxygen levels at baseline, making it a vulnerable target for ischemia.

The ischemia model and the clinical course of CIN, however, differ from those of other ischemia-based pathophysiological processes. Recovery time from renal injury associated with CIN is generally a few days, whereas that for acute tubular necrosis due to other causes is several weeks. This difference suggests that CIN may have a different pathological mechanism or be due to a combination of factors rather than to ischemia alone.

Other mechanisms most likely are contributors in the ischemia model, or their activities are directly cytotoxic to renal cells. Results from research in animals and in vitro suggest that some contrast agents can directly induce caspase-mediated apoptosis of renal tubular cells. Most likely this programmed cell death is due to the activation of shock proteins and the concurrent inhibition of cytoprotective enzymes and prostaglandins. Caspases, a class of proteases, are enzymes involved in protein metabolism. Caspases are activated by a variety of proteins involved in inflammation and cellular injury to direct programmed cell death or apoptosis. Contrast material may also increase the activity of the sodium-potassium adenosine triphosphatase pump, leading to an increase in free adenosine. Adenosine is a potent constrictor of arterioles in the renal medulla and may contribute to the mediation of medullary hypoxia. This notion is supported by several studies that have shown some protective effects of adenosine antagonists in CIN. Inhibition of nitric oxide synthesis and a decreased sensitivity to endothelin receptors involved in vasodilatation are well-studied occurrences in the pathophysiology of CIN. Last, the production of free radicals may contribute to CIN, and a wide variety of scavengers of free radicals have been studied.

Clinical and Laboratory Findings

The clinically relevant laboratory tests in CIN include measurement of the serum concentration of creatinine before and after exposure to contrast material. The clinical features of CIN can range from no signs or symptoms of the abnormality to anuria and a need for dialysis. For most patients, the renal failure associated with CIN is non-liguric, mild, and self-limiting. Usually patients are asymptomatic, and the mild elevation of creatinine peaks within 3 to 5 days and returns to normal within 14 days. In a minority of patients, severe renal failure develops, often with a serum creatinine level greater than 5 mg/dL. These patients may have signs and symptoms that include anuria, hypotension or hypertension, hyperkalemia, cardiac arrhythmia, shock, or other manifestations of organ failure, and they may require hemodialysis.

Distinguishing renal failure associated with CIN from other causes of renal failure is important. A thorough assessment is imperative to identify other causes, such as hypovolemia, shock, renal infarct, and renal atheroemboli. CIN should be a diagnosis of exclusion.

Prevention

Some general principles can be applied to reduce the incidence of CIN. First, detecting patients at risk for CIN is important. Detection requires an understanding of the risk factors and the type of procedure and volume of contrast material to be administered. High-volume procedures that require more than 70 mL of contrast medium, such as coronary angiography, are associated with a higher risk for CIN than are low-volume imaging procedures, such as pelvic CT. In addition, alternative imaging techniques should be considered whenever feasible, and closely spaced or repetitive doses of contrast material should be limited. Most authorities recommend at least 72 hours between imaging studies with contrast material when feasible. Ultrasound, magnetic resonance imaging, and plain radiography may be reasonable imaging alternatives when the risk for CIN outweighs the benefit of using contrast material.

Several therapeutic regimens for the prevention of CIN have been proposed (Table 2). Some experts suggest that simple intravenous hydration with 0.9% saline is adequate therapy for the prevention of CIN. The proposed basis for hydration is expansion of intravascular volume, thereby limiting the proposed effects of renal vasoconstriction and hypoperfusion. Theoretically, hydration increases diuresis, limiting the time contrast material is in contact with the renal tubules, and increases...
intravascular volume, thereby suppressing the renin-angiotensin cascade responsible for renal vasoconstriction.40 Results from clinical trials43,46 have indicated a modest benefit from intravenous hydration and concomitantly deleterious effects from the use of diuretics such as furosemide and mannitol. In the largest trial,43 compared with the control group, patients given saline had a significant decrease in the incidence of CIN; the effect was the most pronounced in patients who had diabetes mellitus. Saline had no effect, however, on patients with marked renal dysfunction, defined as a serum creatinine level greater than 1.6 mg/dL, an important limitation.

Both the route and choice of fluid have been studied. Isotonic fluids, such as 0.9% saline, had greater efficacy than hypotonic solutions in a limited number of trials.50,51 Likewise, intravenous administration was better than the oral route.47

Of note, the data on hydration before administration of contrast material are conflicting. Several studies have shown no benefit, whereas others have shown modest to moderate benefit. The therapeutic regimens, definition of CIN, volume of contrast material, and populations of patients have varied, including anything from a single bolus to 12 hours of preparatory hydration. Nevertheless, intravenous hydration is generally safe with few side effects and is typically well tolerated. The pooled results4,29,31,40,46 indicate at least modest effects in preventing CIN in several at-risk populations. The disadvantage of using hydration is the length of time required to administer the fluid and the risk for volume overload. Although the optimal hydration strategy is yet to be established, typical protocols involve the use of either 0.45% or 0.9% saline infused at a rate of 1 mL/kg per hour for 12 hours before and 12 hours after the administration of contrast material.

Sodium bicarbonate is another compound used to prevent CIN. The administration of sodium bicarbonate alkalinizes the urine, a change that may reduce the production and increase the neutralization of oxygen free radicals.4,28,48 The results of several randomized controlled trials34,38,48 have indicated that sodium bicarbonate is modestly better than 0.9% saline for hydration. Similar to the studies of hydration with isotonic saline, other trials with sodium bicarbonate hydration have had inconclusive results or have indicated no effect.34,40,48 Again, the investigators used different regimens, injected various volumes of contrast material, or did not include adequate controls. Thus, any advantage of using sodium bicarbonate with or without other preventive methods is unclear. In addition, use of sodium bicarbonate is associated with some risk. Some patients, such as those with congestive heart failure and/or left ventricular dysfunction, may have adverse consequences if they are given a large volume of sodium bicarbonate. In addition, administration of sodium bicarbonate is associated with some potentially adverse side effects, including alkalemia, volume overload, and hypocalcemia with or without tetany. A variety of protocols have been

### Table 2: Strategies to prevent contrast-induced nephropathy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion of 0.9% saline at 1 mL/kg per hour 12 hours before and 12 hours after administration of contrast material</td>
<td>Procedure is inexpensive, safe in most patients, easy to perform, and has limited adverse effects</td>
<td>Procedure is not practical in emergency situations (requires 24 hours) and can cause volume overload</td>
</tr>
<tr>
<td>Infusion of 150 mEq of sodium bicarbonate in 1 L of 5% dextrose at a rate of 3 mL/kg per hour for 1 hour before contrast material is administered and then at a rate of 1 mL/kg per hour for 6 hours after contrast material is given</td>
<td>Protocol may be practical in emergency settings (requires 1 hour), could decrease length of stay, and lower volumes of fluid are needed</td>
<td>Adverse effects include volume overload, alkalemia, hypocalcemia</td>
</tr>
<tr>
<td>Oral N-acetylcysteine 600 mg by mouth twice a day the day before and the day of administration of contrast material</td>
<td>Route of administration is oral</td>
<td>N-acetylcysteine has a strong odor and is poorly tolerated, adverse effects are common, and procedure requires 24 hours</td>
</tr>
<tr>
<td>Intravenous N-acetylcysteine 600 mg 30 minutes before administration of contrast material</td>
<td>Protocol can be used in emergency situations, time required is short, and smaller volumes of fluid are needed</td>
<td>Anaphylactoid reactions may occur, cost of protocol is higher than that of others, and availability of intravenous N-acetylcysteine is low</td>
</tr>
</tbody>
</table>
used; the most common is 150 mEq of sodium bicarbonate in 1 L of 5% dextrose administered at 3 mL/kg per hour for 1 hour before the contrast material is injected and then at 1 mL/kg per hour for 6 hours after the imaging study. The solution can be prepared by mixing 150 mL of 8.4% sodium bicarbonate with 850 mL of 5% dextrose, depending on local protocol.

N-acetylcysteine is a thiol-containing tripeptide with several medical uses, including use as a mucolytic agent and treatment of acetylmorphine poisoning. N-acetylcysteine is also used to prevent CIN, purportedly as both an antioxidant and a vasodilatory agent. This tripeptide is one of the most widely studied pharmaceuticals for the prevention of CIN. More than 30 clinical studies and a variety of meta-analyses and reanalyses of its effects in the prevention of CIN have been published. The data on N-acetylcysteine are conflicting, but the differences in results may be related to the wide variance in study protocols, such as use of oral regimens and intravenous regimens and different populations of patients and volumes of contrast material. 

The largest meta-analysis to date included 41 studies and indicated that N-acetylcysteine was efficacious and better than both saline and sodium bicarbonate. The supporting evidence is conflicting, and more study is required before use of N-acetylcysteine can be recommended. Disadvantages of using N-acetylcysteine include its marked sulfurous, rotten-egg odor and the side effects of nausea and vomiting. Patients’ tolerance can be poor, and many require antiemetics when given oral doses. Intravenous doses are also associated with some nausea and vomiting and can cause an anaphylactoid response with urticaria, wheezing, and hypotension.

The most widely accepted regimen is 600 mg of N-acetylcysteine orally twice daily the day before and the day of the administration of contrast material. Intravenous administration of N-acetylcysteine has also been used as a one-time dose immediately before the dose of contrast agent. Again, regimens vary from institution to institution, and use should be guided by local protocol.

A variety of other pharmaceuticals to prevent CIN have been studied, including free-radical scavengers such as ascorbic acid and renal vasodilators such as dopamine, theophylline, and fenoldepa. The success of these agents has been limited. Hemodialysis, an invasive measure effective in removing iodinated contrast materials from the circulation, has been proposed as a treatment for CIN. The results of studies on the use of hemodialysis in prevention of CIN are conflicting, and the invasiveness and risks associated with the procedure limit its role in the management of CIN.

**Treatment**

Information on treatment of CIN is limited. CIN should be a diagnosis of exclusion in patients who experience renal failure after administration of contrast material. Low-flow states, shock, acute tubular necrosis, and interstitial nephritis are more common causes than is CIN. As previously mentioned, most cases of CIN are self-limiting. Maintaining hydration and limiting further renal injury are the mainstays of management for patients with CIN, and no specific antidote or treatment is available.

Treatment consists of intravenous hydration with 0.9% saline, oral fluid intake, and avoidance of potentially harmful therapeutic agents such as nonsteroidal anti-inflammatory drugs or repeat exposure to contrast material. In the rare cases in which renal failure is not resolving, patients are becoming anuric, and electrolyte imbalance and multisystem organ failure are evident, hemodialysis may be required, although the risk-benefit ratio needs to be carefully assessed.

**Nursing Implications**

More and more CT studies are being performed annually, and nurses are at the forefront of preparing, treating, and educating patients about the procedures. Critical care nurses are integral to the determination of which patients are at risk for CIN, the implementation of preventive measures, and the evaluation of patients for the onset of CIN. Patients who are undergoing a repeat CT scan or angiographic procedure are an example. Discussing the feasibility of delaying a study or using another imaging technique such as ultrasound or magnetic resonance imaging with a patient’s care team is imperative.

Nurses can identify patients at risk and work collaboratively to suggest preventive protocols and to ensure that the protocols are carried out. Nurses can be proactive in suggesting a change in medication regimen for patients taking angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs who are scheduled for CT procedures. In addition, nurses are generally the hands-on care providers who will be the first to notice a change in a patient’s...
signs and symptoms, detect oliguria or anuria, and recognize derangements in laboratory findings, such as an increase in the serum level of creatinine or a decrease in GFR.

Critical care nurses are crucial to ensuring that patients are monitored and treated for CIN and are an important aspect of the collaborative care for patients undergoing studies and procedures that require contrast material. Last, critical care nurses can educate patients and patients’ families about CIN and provide teaching and reassurance about the course of the nephropathy.

Conclusion
CIN is an iatrogenic disorder characterized by generally mild and transient renal injury after the injection of iodinated contrast agents. CIN is generally self-limiting but can be severe and, in some patients, may result in prolonged hospitalization, increases in morbidity and mortality, and the need for invasive measures such as hemodialysis. Prevention of CIN includes identifying at-risk patients and considering use of alternative imaging techniques or contrast materials. For patients who require iodinated contrast material, several pharmacological protocols to prevent CIN have been suggested, including infusions of sodium bicarbonate, N-acetylcysteine, and physiological saline. Critical care nurses can be proactive in helping detect patients who may be at risk for CIN and in identifying preventive strategies for patients who are at risk for the nephropathy. CCN

Financial Disclosures
None reported.

References


