Review

Contrast-Induced Nephropathy

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Contrast-induced nephropathy has become a significant source of hospital morbidity and mortality with the ever-increasing use of iodinated contrast media in diagnostic imaging and interventional procedures such as angiography in high-risk patients. It is the third most common cause of hospital-acquired acute renal failure, after surgery and hypotension [1]. In this clinical setting, radiologists must develop an ability to recognize predisposing risk factors, to institute appropriate preprocedural prophylactic treatments, and to have a knowledge of the clinical presentation and subsequent management of the condition.

Several authors have published in-depth review articles: most notably Katzberg [2], who performed a thorough review of urologic contrast agents and their potential effects, and Tublin et al. [1], who published a review in 1998 of current concepts relating to contrast nephropathy. Although many of their concepts still hold true, we intended to concentrate on risk-factor analysis and an updated and comprehensive review of current prophylactic agents, areas that, to date, have not, to our knowledge, been fully addressed while also providing a general overview of the issues relating to contrast-induced nephropathy that may be relevant to the modern radiologist.

Definition

Contrast-induced nephropathy is most commonly defined as acute renal failure occurring within 48 hr of exposure to intravascular radiographic contrast material that is not attributable to other causes [3]. Ideally, the impairment of renal function should be measured by serial creatinine clearance, but because this step may be neither practical nor cost-effective in many centers, most of the literature describes the use of isolated measurements of serum creatinine levels, even though this parameter may be less sensitive at reflecting subtle early changes in renal function and may be slower to reach maximal sensitivity than creatinine clearance. Serum creatinine levels may prove to be more sensitive, however, in cases of preexisting renal impairment, in which tubular secretion of creatinine can lead to overestimation of the glomerular filtration rate (GFR).

An arbitrary range of values of between 25% and 50% (an increase in absolute values of 0.5–1.0 mg/dL) increase in serum creatinine levels from baseline has been suggested to define contrast-induced nephropathy [2, 4]. Other suggested definitions include the following: a rise in serum creatinine levels of more than 100%, a rise in serum creatinine levels of more than 1 mg/dL, a postprocedural serum creatinine level greater than 5 mg/dL, or acute renal failure requiring dialysis [5]. Lautin et al. [6] used six separate definitions with criteria ranging from an increase in creatinine level of more than 0.3 mg/dL to an increase of 2.0 mg/dL or more and found the more restrictive higher cutoff point to be less sensitive for predicting incidences of contrast-related renal dysfunction. Although it has been argued that a low increment of change of serum creatinine levels may not be clinically important, this low increment allows studies of reasonable sample size [3]. In addition a large cohort study by Levy et al. [7] has shown that even apparently small decreases in renal function can lead to excessive mortality rates independent of other risk factors, and given that small rises in serum creatinine levels actually represent a significant drop in GFR, a definition set at the lower end of the accepted range has become the most commonly quoted. Hayman [8] has suggested that changes of 0.3 mg/dL are not statistically significant in many laboratories; hence contrast-induced nephropathy has become most commonly defined as "a 25% increase in serum creatinine concentration from the baseline value, or an absolute increase of at least 0.5 mg/dL (44.2 μmole/L), which appears within 48 hours after the administration of radiographic contrast media, and is maintained for 2–5 days" [9].

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This definition may in part account for the large number of cases reported showing only transient elevations of serum creatinine levels or at least elevations that do not require dialysis. Although this large number has led to questioning of the clinical relevance of such rises, these subtle changes have been shown to be associated with significant morbidity rates [7] and, in addition, may help to identify those with borderline renal function who may be at risk of developing fulminant renal failure in the future.

Clinical Features and Treatment

Urinary epithelial cell casts, debris, and urate and calcium oxalate crystals are nonspecific findings in contrast-induced nephropathy [1, 10]. Low urinary sodium and fractional excretion of sodium (< 1%) have been reported as being distinctive characteristics of this condition [2, 11], but these findings have not consistently been shown to be specific for contrast-induced nephropathy [12]. A persistent nephrogram on radiography or CT 24 hr after contrast administration is also said to be suggestive of a diagnosis of contrast-induced nephropathy [13, 14] but is not a consistent or a specific finding [8, 15].

Contrast-induced nephropathy most commonly manifests as a nonoliguric and asymptomatic transient decline in renal function [16]. The serum creatinine level begins to rise within 24 hr of contrast administration, usually peaks within 3–5 days, and returns to baseline within 10–14 days [11, 17]. Oliguric acute renal failure requiring hemodialysis can also occur. This condition presents with oliguria (24-hr urine volume < 400 mL) within 24 hr of contrast administration and typically persists for 2–5 days. Serum creatinine levels peak within 5–10 days and return to baseline within 14–21 days [2]. Morbidity and mortality rates are significantly higher in this group of patients when compared with those who have nonoliguric renal failure [16].

Treatment of established contrast-induced nephropathy should start with the recognition of renal impairment after the study. In patients at higher risk, renal function should be carefully monitored by measuring serum creatinine levels before and once daily for 5 days after the radiographic procedure. After contrast-induced nephropathy is identified, the subsequent management of this condition is the same as that for acute renal failure due to other causes. Admission to the hospital and subsequent judicious monitoring of serum electrolyte levels are required to prevent hyperkalemia, hyponatremia, hyperphosphatemia, hypocalcemia, hypermagnesemia, and metabolic acidosis associated with acute renal failure. Appropriate nutritional support is essential and strict recording of patient weight and fluid input–output is required until creatinine levels return to baseline. High phosphate levels can be treated using phosphate binders such as calcium carbonate; hyperkalemia is treated by dietary restriction and potassium-binding resins or insulin–dextrose infusion when the potassium level is greater than 6.5 mmol/L. Correction of acidosis may require oral sodium bicarbonate. More severe cases may require temporary hemodialysis, but a minority of patients who do not respond to conservative treatment will require permanent dialysis or kidney transplantation [18].

Epidemiology

The rate of incidence of contrast-induced nephropathy as a complication of radiographic diagnostic and interventional studies varies markedly, depending on the definition used and on other variables such as the type of radiology procedure performed, the dose and type of contrast agent administered, the differing patient populations in regard to number and type of risk factors, and the length of patient follow-up. An overall incidence of 14.5% was recently quoted in a large epidemiologic study [5] (defined as > 25% increase in serum creatinine levels over baseline in the first 5 days), but rates may vary from 0% to 90%, depending on the presence of risk factors, most notably chronic renal insufficiency, diabetes mellitus, and high contrast volume administered [4, 19–28]. Incidence among patients with diabetes has been reported to be 9–40% in patients with mild-to-moderate chronic renal insufficiency and 50–90% in those with severe chronic renal insufficiency [29, 30]. In contrast, the incidence in the general population is much lower and has been calculated to be less than 2% [31].

Despite a lack of consensus as to exact rates and definitions, contrast-induced nephropathy remains a significant source of morbidity and mortality. Even with advances in medical care, the overall rate of hospital-acquired acute renal failure, of which contrast-induced nephropathy is the third most common cause (10% of cases), has not improved, remaining at approximately 5% of hospital admissions [32]. Mortality rates associated with acute renal failure have also remained high, averaging approximately 30% for toxin-induced failure [18]. McCullough et al. [5] quoted an in-hospital mortality rate of 35.7% for patients undergoing coronary angiography and an 18.8% 2-year-survival rate. Regardless of the high number of comorbidities in this patient cohort, Levy et al. [7] had similar findings in a study of more than 16,000 patients undergoing contrast-enhanced examinations (CT of the head and body, cardiac angiography, and peripheral angiography). They showed that in the 1% of patients (n = 174) who developed contrast-induced nephropathy (defined as an increase of serum creatinine levels of ≥ 25% above baseline), there was a significantly higher mortality rate than in the patient group from the same population matched for age and baseline creatinine levels who underwent similar contrast-enhanced procedures but did not develop renal failure (34% vs 7%). The overall mortality rate for the cohort was 0.4%, with 0.1% requiring renal replacement therapy. Contrast-induced nephropathy was thus found to result in excessive mortality rates, independent of other risk factors. The authors also found that not only does the condition increase the risk of death from preexisting nonrenal conditions, but it is also associated with major nonrenal morbidity rates from acquired sepsis, bleeding, coma, or respiratory failure.

Pathogenesis

The exact underlying mechanisms of nephrotoxicity have yet to be fully elucidated but are likely to involve the interplay of several pathogenic factors (Fig. 1). Intrinsic causes include the following: increased vasoconstrictive forces, decreased local prostaglandin- and nitric oxide (NO)-mediated vasodilatation, a direct toxic effect on renal tubular cells with damage caused by oxygen free radicals, increased oxygen consumption, and increased intratubular pressure secondary to contrast-induced diuresis, increased urinary viscosity, and tubular obstruction, all culminating in renal medulla ischemia [33–35]. Intrinsic causes act in concert with harmful extrinsic (prerenal) causes such as dehydration and decreased effective intravascular volume.

Laboratory animals have not been shown to have renal failure when given radiographic contrast agents unless the systemic and renal circulation is compromised in some way. Brezis and Rosen [36] have speculated that

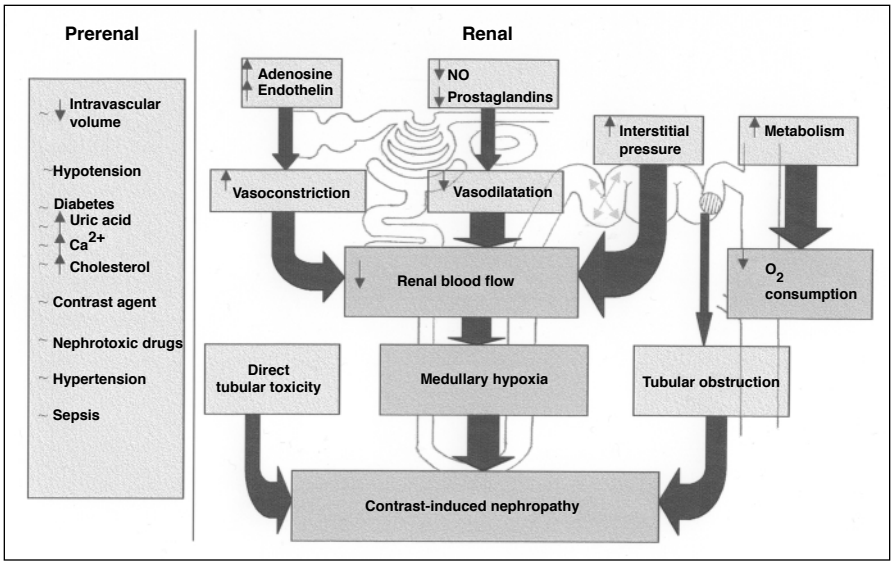

Fig. 1.—Diagram shows proposed pathophysiologic mechanisms of contrast-induced nephropathy. NO = nitric oxide.

such renal failure occurs because of vulnerability of the renal medulla circulation to stimuli that disrupt the balance between the high metabolic needs of the tubular segments of the renal medulla and their hypoxic environment. This balance is normally maintained by the interplay between vasodilator and vasoconstrictor influences, mediated by the activity of NO, prostaglandin, and endothelin systems within the medulla. After the injection of radiographic contrast media, there is a transient increase, followed by a more prolonged decrease, in renal blood flow [37–40]. This change is caused by the disruption of the aforementioned normal physiologic balance as a result of the delivery of a large hyperosmotic load to the juxtaglomerular apparatus [41], or it may be caused by systemic mediators such as atrial natriuretic peptide (ANP) and antidiuretic hormone. Endothelin-1 has been implicated as the most likely causative agent in a number of studies [42, 43], but a clinical trial of an endothelin-receptor antagonist failed to show a protective effect [44].

An intrarenal hypoxia ensues, which is directly related either to the hemodynamic changes or to the increased tubular energy expenditure due to osmotic stress [45, 46]. This stress may not be tolerated if renal circulation is compromised—for example, in patients with diabetes and renal failure (who are at highest risk of contrast-induced nephropathy) in whom medullary hypoxia and impaired endothelium-derived vasorelaxation are already present.

Intratubular contrast agents lead to tubuloglomerular feedback and increase renal adenosine concentrations as a result of enhanced adenosine triphosphate hydrolysis. Adenosine has been found to enhance the renal hemodynamic effects of contrast media, resulting in local renal vasoconstriction [47]. Blockage of vasodilatory prostaglandin production by indomethacin and sodium depletion have both been shown to increase the adenosine effect in the kidneys [48–50]. Renal ischemia before contrast application increases the toxicity of prostaglandin blockade [51] and enhances adenosine generation, leading to renal vasoconstriction [52]. Both adenosine and contrast material show disparate effects regarding regional blood flow of the kidney with medullary vasodilation [39, 53]. Animal experimental models that revealed a nephroprotective effect of adenosine antagonism (using either theophylline or aminophylline) corroborate these findings [54–57].

Reactive oxygen species have also been implicated as a contributing factor and may be the cause of the vacuolization of epithelial cells in the proximal tubules [58]. There is evidence that renal free-radical production is increased after contrast administration [44, 59, 60], whereas infusion of superoxide dismutase and allopurinol, each of which should reduce free-radical content, have been reported to ameliorate contrast-induced hypoperfusion [61]. Although lipid peroxidation and tubular oxidative damage could presumably lead to transient renal dysfunction, definitive experimental evidence confirming the role of renal oxidative damage in contrast nephropathy remains sparse [35, 62].

Risk Factors

Many factors have been reported as influencing contrast-induced nephropathy (Appendix 1), but few have been proven to be independent risk factors [63]. However, it has been recommended that every known risk factor should be analyzed to properly evaluate a total cumulative risk of developing contrast-induced nephropathy because total risk rises as the number of risk factors increase [19, 27, 64].

Preexisting Impairment of Renal Function

Irrespective of cause, preexisting impairment of renal function appears to be the most important risk factor [4]. In one study, for example, 50% of patients with a creatinine level of 176 μmol/L (2 mg/dL) had a deterioration in renal function [65]. Similarly, in two studies of a population with a baseline serum creatinine concentration averaging 2.5 mg/dL (220 μmol/L), contrast-induced nephropathy was a complication in 30–50% of patients [21, 25]. Davidson et al. [66], in a series of 1,144 patients undergoing cardiac catheterization, found a low risk of contrast-induced nephropathy (defined as an increase of serum creatinine levels of ≥ 0.5 mg/dL) in patients with normal renal function, but a high risk in those with preexisting azotemia (serum creatinine levels > 1.2 mg/dL). The risk increased exponentially with serum creatinine concentration (e.g., 20% incidence in those with a serum creatinine levels of 2.0 mg/dL [177 μmol/L]). Moore et al. [67] found a highly significant relationship ($p <$ 0.001) between an increasing baseline level of serum creatinine and the frequency of nephrotoxicity (varying from 2% in those with baseline creatinine of < 1.5 mg/dL to 20% in those with levels of > 2.5 mg/dL).

Diabetes Mellitus with Associated Renal Insufficiency

Diabetes mellitus with associated renal insufficiency has been identified as an independent risk factor for contrast nephropathy, with as many as 56% of those who develop the condition progressing to irreversible renal failure. In addition, patients with diabetes who have advanced chronic renal failure (serum creatinine levels > 3.5 mg/dL) due to causes other than diabetic nephropathy are at significantly higher

risk of developing contrast-induced nephropathy [30].

Some authors have suggested that diabetes alone may be an independent risk factor for the development of contrast-induced nephropathy [9]. More recent research has failed to corroborate this connection. For example, Parfrey et al. [4], in a prospective trial of patients with diabetes, showed that none of 85 patients with diabetes and normal renal function developed clinically significant renal impairment (defined as an increase of > 50% in serum creatinine levels). However, given that those with diabetes alone were found to be at slightly higher risk of renal failure than the general population, it seems prudent to include diabetes in a preprocedural risk assessment.

Nephrotoxic Drugs

Directly nephrotoxic drugs (e.g., cyclosporin A, aminoglycosides, amphotericin, and cisplatin) and those that inhibit the local vasodilatory effects of prostaglandins (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]), have been reported to render the kidney more vulnerable to nephrotoxic contrast agents [9, 28, 68]. NSAIDs may lead to acute tubulointerstitial nephritis, and long-term ingestion of large amounts can lead to chronic tubulointerstitial nephritis. Many other drugs including penicillins and sulfonamides can also induce an acute tubulointerstitial nephritis, whereas aminoglycoside antibiotics exert a direct nephrotoxic effect, their combination with furosemide being particularly potent [69]. Cyclosporin A is a direct cellular toxin that impairs lysosome function in both the proximal and distal tubules, evoking tubulointerstitial changes, and platinum derivatives such as cisplatin attach to sulfhydryl groups and impair proper enzyme function [9]. Although all these medications are known to induce renal damage, their individual roles as independent risk factors of contrast-induced nephropathy have yet to be determined in large prospective clinical trials.

Reduction of Effective Intravascular Volume

Reduction of effective intravascular volume (due to congestive heart failure, liver cirrhosis, or abnormal fluid losses), prolonged hypotension (especially when induced by intensive antihypertensive treatment combined with angiotensin-converting enzyme inhibitors and diuretics, most notably furosemide), and dehydration have been reported as contributing to prerenal reduction in renal perfusion, thus enhancing the ischemic insult of contrast media [3, 10, 14, 17, 68].

Multiple Myeloma

Multiple myeloma has been reported as a risk factor for contrast-induced nephropathy. It has been argued that high amounts of protein in the tubular lumen with concomitant contrast material load may cause an obstructive nephropathy, a mechanism that is thought to be central to the development of renal insufficiency in patients with nephrotic-range proteinuria secondary to multiple myeloma [70, 71]. The pathomechanism of this process has been explained by the precipitation of radiographic contrast molecules, together with Tamm-Horsfall proteins and other abnormal proteins, tubular epithelial cells damaged and desquamated as a result of ischemia, direct contrast toxicity, or disturbed function of integrins [72]. However, given that acute renal failure rarely occurs after contrast administration if dehydration is avoided [69] and that a review of seven retrospective studies showed an incidence of contrast-induced nephropathy of only 0.6–1.25% in patients with myeloma, it seems unlikely that multiple myeloma in the absence of other risk factors confers excessive risk of development of contrast-induced nephropathy [3, 10, 73]. Despite this rare likelihood, because of the hyperuricemia, hypercalcemia, volume depletion, amyloidosis, and light chain nephropathy associated with multiple myeloma, patients are at increased risk of renal failure for reasons other than those associated with contrast administration [74] and should be included as part of a risk assessment. The importance of hypercalcemia, hyperuricemia, and proteinuria per se as independent risk factors is not clear [28, 68].

Volume and Timing of Contrast Administration

Large doses and multiple injections of contrast media within 72 hr increase the risk of the patient's developing contrast-induced nephropathy [27, 68, 75]. The lethal dose, 50% (LD_{50}) of diatrizoate, a high-osmolar contrast medium (HOCM), in mice is estimated at 7.6 g I/kg [76], whereas a lethal dose of iohexol, a low-osmolar contrast medium (LOCM), is 24.2 g I/kg, but unfortunately mouse LD_{50} values do not directly predict how contrast media will affect the human kidney [77]. Definitive cutoff levels have not been established, but Manske et al. [30] reported that volumes of LOCM (iohexol or iopamidol) greater than 30 mL were associated with markedly increased incidence of contrast nephropathy (defined as 25% increase in serum creatinine levels within 48 hr), and for each 5-mL increment, the risk of nephropathy increased 65%. Mean volumes administered range from 30 to 140 mL in various studies of LOCM [3, 6, 10, 30, 44].

Route of Administration

The route of administration is also important, with contrast media being more nephrotoxic when administered intraarterially [68]. This effect is thought to be due to the fact that the acute intrarenal concentration of contrast media is much higher after intraarterial rather than IV injection.

Osmolarity

Similarly, the osmolarity of the contrast media plays an important role with large clinical studies and meta-analyses indicating that the use of an LOCM substantially reduces the risk of nephropathy in high-risk patients compared with the use of HOCM (see section on Contrast Media under Preventative Treatments) [11,16, 78–80]. However, this benefit could be shown only in patients with preexisting renal dysfunction in whom contrast material was administered intraarterially. In contrast, no benefit was found among those with normal renal function (with or without diabetes) in whom contrast material was given by IV [80]. A recent study suggests that iodixanol, a nonionic dimeric isoosmolar contrast medium (IOCM) with lower toxicity than LOCM, is of significant benefit in a group of patients known to be at high risk for the development of contrast-induced nephropathy [81]. However, further clinical trials are indicated to establish properly the role of contrast osmolality as a risk factor independent of the mode of administration.

Advancing Age

Advancing age is reported to predispose patients to renal sodium and water wasting due to reduction in renal mass, function, and perfusion [27, 68].

Sepsis and Others

Sepsis, through direct damage by bacterial toxins to renal tubules and impairment of circulation, has also been reported as a risk factor, as have hypertension, peripheral vascular disease, and atopic allergy [9, 27, 82].

Risk Factor Summary

Although all the previously mentioned factors may theoretically predispose the patient to contrast-induced nephropathy, the only confirmed independent risk factors are preexisting azotemia and renal impairment

with associated diabetes mellitus. The effects may be additive, however, and given that many of these factors are highly prevalent among patients requiring diagnostic and interventional procedures [83, 84], they should be considered in the proper risk assessment of patients for the development of contrast-induced nephropathy.

The European Society of Urogenital Radiology [85] recommends that only elevated serum creatinine levels (particularly secondary to diabetic nephropathy), dehydration, congestive heart failure, age greater than 70 years, and concurrent nephrotoxic drugs be used to establish risk. However, the use of a more comprehensive preprocedural assessment may be warranted, particularly in the high-risk inhospital population undergoing interventional radiology procedures such as angiography (see proposed protocol, Fig. 2). Cochran et al. [27] presented a point system (tally of risk factors) model to predict the probability of developing contrast-induced renal insufficiency (defined as a risk in serum creatinine levels of > 0. 3 mg/dL or > 20% increase from baseline within 5 days) in their cohort of 266 patients undergoing renal angiography. Odds ratio analysis identified 10 risk factors that were associated with a significantly increased risk of developing contrast nephropathy (age, sex, abnormal baseline serum creatinine levels, proteinuria, amount and type of contrast material, undergoing two contrast studies within 72 hr, hypertension, vascular disease, and preexisting renal disease). Using logistic regression analysis, Cochran et al. found five risk factors that were shown to predict at-risk patients with high probability; the other significant factors in the odds ratio analysis were deemed unnecessary because they were strongly related to the five included (age > 55 years, proteinuria, abnormal baseline serum creatinine level, the use of HOCM [meglumine diatrizoate], and preexisting renal disease). These authors showed that the probability of developing the condition increased as the number of factors increased, with the most marked jump in serum creatinine levels seen when three or more risk factors were present (from < 5% increase with two factors to > 30% increase with three factors). To the best of our knowledge, no further investigations of the worth of this model in different patient populations have been published. We believe that the study by Cochran et al. may have merit in helping to identify at-risk patients, and we have thus adapted their approach to encompass those risk factors that are most commonly quoted in the literature but have not yet been definitively proven as being independent. We propose that preexisting renal impairment alone or three or more of the risk factors listed (Fig. 2) pose a significant risk for developing contrast-induced nephropathy.

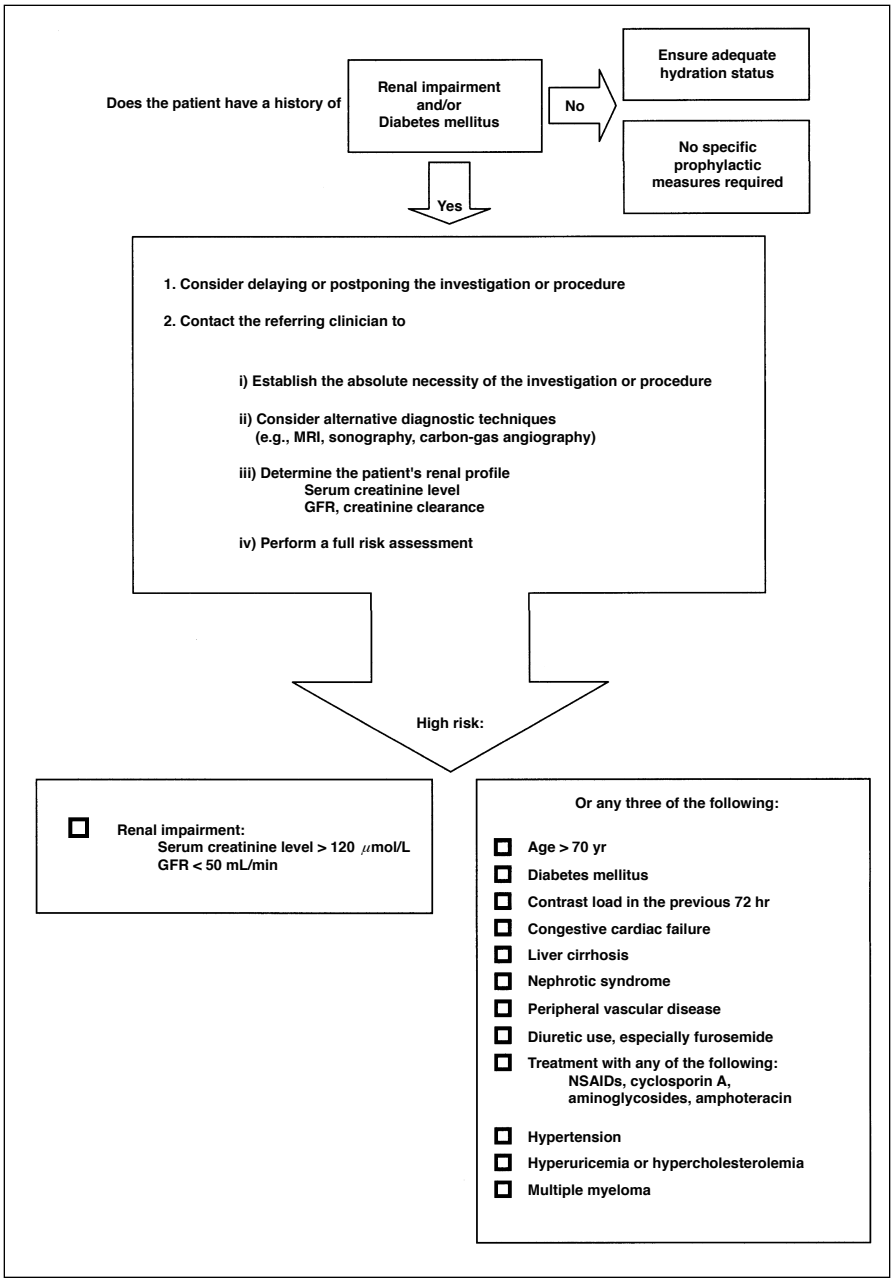

Fig. 2.—Diagram shows proposed radiology department protocol for prevention of contrast-induced nephropathy. Maximum risk is renal impairment, diabetes, and other risk factors. High risk is renal impairment, diabetes only, and three or more cumulative risk factors. Low risk is less than three risk factors. GFR = glomerular filtration rate, NSAIDs = nonsteroidal antiinflammatory drugs.

For patients undergoing routine contrast-enhanced investigations such as CT in a busy modern radiology department, it may not be feasible to perform an exhaustive risk assessment on every patient. In this situation, questioning in regard to a history of diabetes or renal impairment or both may be used as a quick screening questionnaire. Along with accurate clinical details from the referring physician, this simple questionnaire could be included with the outpatient appointment card and may be used to identify those most at risk for contrast-induced nephropathy. The pro-

posed preprocedural checklist (Appendix 2) may also be used to incorporate more general information such as the date of last menstrual period, the use of metformin in patients with diabetes, and history of allergic reactions. These assessment models have not been validated but may prove useful as a template to allow radiologists and clinicians alike to increase awareness and identification of contrast-induced nephropathy.

Preventive Treatments

Several drug interventions based on one or more of the pathogenic mechanisms outlined in the Pathogenesis section have been tested in trials for prophylaxis against the development of contrast-induced renal dysfunction. These are outlined in the following section but have generated few resoundingly positive results, and subsequently these treatments are not widely used. At present, only IV hydration and avoidance of nephrotoxic drugs are widely used to decrease the incidence of contrast-induced nephropathy.

General measures to minimize the incidence of nephropathy include carefully considering whether the contrast examination is absolutely needed, especially in high-risk patients; using the minimal effective dose; and eliminating potentially nephrotoxic drugs (e.g., NSAIDs, aminoglycoside antibiotics, cisplatin, cyclosporin A, and amphotericin B) at least 24 hr before the study. The order of nil by mouth after midnight should be abolished in modern radiology departments in favor of protocols that allow clear liquids up to 2 hr before the procedure and that encourage IV hydration. Alternative diagnostic procedures should be considered in those at high-risk—for example, sonography and MRI. Interventional radiologists also have the option of using CO_2 angiography in high-risk patients, a luxury not afforded to cardiologists, neurointerventionalists, or those supervising CT studies.

Hydration

Adequate hydration is the simplest and most effective way of protecting renal function. High-risk patients should be administered 0.9% saline by IV infusion at a rate of approximately 1 mL/kg per hour, adjusted appropriately for the patient's current fluid status and cardiovascular condition. This treatment should be commenced 6–12 hr before the procedure and continued for up to 12–24 hr after the radiographic examination, if diuresis is appropriate. Although clinical studies have not shown uniformly that dehydration is a definite risk factor, iodinated contrast agents increase urine volume and osmolar clearance, and their effect on the kidney is prolonged by the decrease in both renal blood flow and GFR seen in dehydrated states [2].

Eisenberg et al. [86] in a retrospective study of 537 patients reported that contrast-induced nephropathy (defined as an increase of blood urea nitrogen of 50% or 20 mg/dL or an increase in serum creatinine levels of 1 mg/dL within 24 hr or both) was avoided by the administration of 550 mL of normal saline and 250 mL of heparinized saline flush per hour during the 295 cerebral and 242 abdominal or peripheral angiograms. Contrast doses varied with an average of 115 mL of meglumine iothalamate (Conray-60, Mallinckrodt) being administered for cerebral angiograms and an average of 210 mL of either meglumine iothalamate, diatrizoate, or metrizoate being administered for abdominal and peripheral studies, giving a total HOCM dose of 1–5 mL/kg. These markedly differing doses of contrast agent weakened the study, as did the lack of a control group, failure to control for intravascular volume, and the lax criteria used for diagnosis of renal failure.

A report of a subsequent retrospective analysis of 518 patients with impaired renal function (serum creatinine levels > 1.9 mg/dL) reported that the 76 patients who developed contrast-induced nephropathy (defined as an increase in serum creatinine levels > 0.5 mg/dL over 48 hr) had lower blood pressure before angiography and had less hydration before the procedure than 82 matched controls [87]. Solomon et al. [22] conducted a prospective trial in 78 patients with chronic renal insufficiency in whom simple fluid therapy (1 mL/kg per hour of 0.45% saline for 12 hr before and after coronary angiography) was shown to be beneficial in reducing renal dysfunction after contrast administration. Further trials in patients undergoing angiography have shown a lower frequency of nephropathy in studies using a hydration protocol compared with studies without mandatory hydration [66]. Similarly, in an uncontrolled study of 25 patients with chronic renal insufficiency (serum creatinine levels > 1.8 mg/dL), no patients who received intraoperative hydration (550 mL/hr of 0.9% saline) developed renal dysfunction [88].

More recently a prospective, single-center randomized trial of 119 patients by Merten et al. [89] has suggested that the use of sodium bicarbonate hydration is superior to sodium chloride hydration. Rates of contrast-induced nephropathy were significantly lower in the sodium bicarbonate group (1.7%, $n = 1$) when compared with the sodium chloride group (13.6%, $n = 8$) when both cohorts were administered 154 mEq/L of either solution IV. Although somewhat limited by its small sample size, dropout rates, and its single-center nature, the authors argue that the bicarbonate ion is more efficacious than chloride, a fact that they say is backed up by animal research. Merten et al. suggest that free-radical formation (which is promoted by an acidic environment) can be inhibited by increasing the pH of normal extracellular fluid, with the use of bicarbonate. Although confirmation of these findings in a larger multicenter trial is required, in the interim sodium bicarbonate hydration could be considered as an effective and safe alternative to normal saline in the prehydration of high-risk patients.

Despite the fact that no controlled randomized trial with sufficient statistical power has been rigorously performed to prove the benefit of hydration as scientific fact, it is almost universally accepted as an appropriate and safe measure to prevent contrast-induced nephropathy.

N-Acetylcysteine

There is some evidence that reactive oxygen species have a role in renal damage caused by contrast agents [35, 44, 60–63]. *N*-acetylcysteine (NAC), a thiol-containing antioxidant, is thought to act either as a free-radical scavenger or as a reactive sulfhydryl compound that increases the reducing capacity of the cell. It may also increase the biologic effects of NO by combining with NO to form *S*-nitrosothiol, which is a more stable form and a potent vasodilator. This interaction may limit the production of the damaging peroxinitrite radical because NAC would compete with the superoxide radical for NO. It also increases the expression of NO synthase and may thus also improve blood flow [90].

NAC has been shown to ameliorate ischemic renal failure in the animal model [91] and has been used successfully to reduce the toxic effects of a variety of experimentally or clinically induced ischemia-reperfusion syndromes of the heart, kidney, lung, and liver [92, 93]. Recent studies have suggested that NAC has vasodilatory properties [94, 95], and it has also been reported to block the expression of vascular cell adhesion molecule-1 and the activation of nuclear factor-κβ in

glomerular mesangial cells [96]. Early administration of NAC has been shown to prevent a reduction in renal function in patients with acetaminophen poisoning who have liver failure [97, 98]. Similarly, a recent nonrandomized study suggested that NAC may improve renal function in patients with hepatorenal syndrome [99].

Tepel et al. [100] found that the incidence of contrast nephropathy after CT in patients with chronic renal insufficiency was greatly reduced with NAC. Just 1,200 mg per day, given orally in divided doses on the day before and the day of administration of the contrast agent, prevented the expected decline in renal function in all patients with chronic renal insufficiency (mean serum creatinine levels, 2.4 ± 1.3 [± SD] mg/dL; creatinine clearance, < 50 mL/min). However, the study was limited by its small number of subjects (n = 83), lack of long-term follow-up, and the fact that some patients had serum creatinine levels in the normal range. Indeed, the serum creatinine criteria for renal impairment were sufficiently low to include potentially patients with normal kidney function in the study. The positive findings in the study by Tepel et al. are encouraging and were supported by results from the Acetylcysteine to Prevent Angiography-Related Renal Tissue Injury trial (54 patients; overall incidence of contrast nephropathy, 28%; risk ratio, 0.18 with 95% confidence interval (CI)) [101]. Two further trials, Allaqaband et al. [102] and Durham et al. [103], had more negative outcomes, most notably Durham et al. in 2002.

Durham et al. [103] suggested that NAC was ineffective in their study of 79 patients undergoing cardiac angiography. Despite these findings, the authors highlighted a number of differences between the ground-breaking study of Tepel et al. [100] and their own. Both studies used nonionic LOCM, but patients in the study of Durham et al. received a slightly higher mean dose (81.6 vs 75 mL) intraarterially as opposed to IV in the study of Tepel et al. The protocol of NAC administration also differed, with Durham et al. giving 1,200 mg 1 hr before the procedure and then 3 hr afterward. Given that oral NAC reaches peak serum levels in approximately 1 hr and has an elimination half-life of 2.1 hr, administration of NAC is unlikely to have resulted in the difference between the two studies. However, the authors admitted that a metabolite of NAC might have antioxidant or other favorable properties that account for the benefits of earlier administration in the study of Tepel et al.

Another negative study by Allaqaband et al. [102] prospectively enrolled 123 patients (85 patients in NAC vs saline-alone groups) who were scheduled for cardiovascular procedures and had a baseline creatinine level greater than 1.6 mg/dL or creatinine clearance of less than 60 mL/min. The authors found that NAC offered no additional benefit over hydration alone. Patients received LOCM and either saline alone or fenoldopam (0.1 μg/kg per minute) plus saline or NAC orally (600 mg) plus saline. No significant difference was found in the incidence of contrast nephropathy (defined as an increase in creatinine level > 0.5 mg/dL after 48 hr) in the three groups (p = 0.919). However, serum creatinine levels decreased after 48 hr (vs baseline) in a higher proportion of NAC patients (38% vs 18% in the fenoldopam group and 15% in the saline group).

Goldenberg et al. [104], in a study of 80 patients in whom somewhat higher-than-standard doses of NAC (600 mg three times a day) were used, found an increase of more than 0.5 mg/dL in serum creatinine levels in 10% of the NAC group versus 8% in the control group. They concluded that prophylactic administration of oral NAC was not justified.

A recent in-depth and comprehensive meta-analysis of all studies to date, including all of those mentioned previously, but excluding Goldenberg et al. [104], has shown that overall, NAC reduces the occurrence of contrast-induced nephropathy after nonionic contrast medium administration by half in high-risk patients [107]. Seven trials including 805 patients found NAC plus hydration reduced the relative risk of contrast nephropathy by 56% (0.435; p = 0.02). In addition, five other studies involving a total of 275 patients were deemed ineligible for inclusion. Three of these reported a significant benefit of NAC.

A limitation of this meta-analysis, however, was that only seven patients (0.7%) required permanent dialysis as a result of contrast-induced renal failure, which again brings into question the clinical relevance of a phenomenon that may be inherently transient. No trial to date has investigated the effect of NAC on hard clinical end points such as in-hospital morbidity rates, mortality rates, or dialysis dependency. A further limitation of the meta-analysis is the suggestion of publication bias, which may overestimate the true treatment effect.

Nevertheless, the overall message of the study by Birck et al. [105] cannot be overlooked. Coupled with a recent study that has shown that NAC may have additional benefits (other than its reported renoprotective effects) in certain patient groups, its popularity as a prophylactic agent has grown. In this study of 134 patients with end-stage renal failure, empiric evidence showed that NAC was found to have a protective role in combating cardiovascular disease in patients undergoing hemodialysis. It showed that of the 134 patients with end-stage renal failure, those in the NAC group had a risk of reaching the primary end point (fatal and nonfatal myocardial infarction, death from cardiovascular disease, need for coronary angioplasty or bypass surgery, ischemic stroke, or peripheral vascular disease with amputation) that was 40% lower than that in the control group [106].

These recent studies, coupled with the favorable side effect profile of NAC and its low cost, mean that NAC has gained favor in many centers as a preventive therapy, particularly in the high-risk group undergoing coronary interventions. Whether the observed reduction in relative risks of an arbitrarily defined increase in serum creatinine level confers benefit in clinical practice is a matter of some debate, but given the association of contrast nephropathy with increased morbidity rates, mortality rates, and in-patient hospital stays, the use of NAC seems justified in high-risk groups. An oral dose of 600 mg twice daily the day before and the day of procedure is the most commonly used regimen. IV doses of 150 mg/kg over half an hour before the procedure or 50 mg/kg administered over 4 hr have more recently been gaining popularity for use in critically ill patients or in those who are unable to take NAC orally [107].

More recently, Briguori et al. [108] reported a protective effect of a high dose (1,200 mg twice daily) versus a standard dose (600 mg twice daily) along with saline hydration. In a cohort of 224 patients with chronic renal insufficiency (creatinine level > 1.5 mg/dL or creatinine clearance < 60 mL/min), there was an increase in the creatinine level of at least 0.5 mg/dL after angiography in 12 (11%) of 109 in the standard group compared with four (3.5%) of 114 in the double-dose group (p = 0.04). The authors also found that the amount of contrast agent used (> or < 140 mL) had a significant effect, with those in the high-dose group benefiting significantly from preprocedural NAC (renal dysfunction reduced from 18.9% to 5.4%, p = 0.04).

Contrast Media

On the basis of their chemical and pharmacologic properties, radiographic contrast

agents can be classified into ionic or nonionic and as monomers or dimers. Improvements in recent years have centered on the principles of eliminating ionicity, lowering osmotoxicity, increasing hydrophilicity, and counting the number of iodine atoms per molecule.

The osmotoxic effect of contrast medium is central to the development of contrast-induced nephropathy and is described in terms of the ratio of iodine atoms to dissolved particles. The higher the ratio, the better the attenuation of X rays because there are more iodine atoms for fewer particles of contrast agent. Media with a ratio of 1.5:1 are HOCM, media with a ratio of 3:1 are LOCM [2], and, most recently, agents with a ratio of 6:1 have been developed and are referred to as IOCM [2]. In one study of 1,196 patients, it was shown that patients receiving HOCM (diatrizoate) were 3.3 times as likely to have nephropathy induced as those receiving LOCM (iohexol) [23]. Subsequently, a meta-analysis of 31 trials (45 trials included, and 14 had data unavailable) concluded that the use of LOCM rather than HOCM was beneficial to patients with preexisting renal failure [81].

LOCM causes less discomfort and fewer cardiovascular and anaphylactic adverse reactions than HOCM but is more expensive. It has been recommended that a high risk for development of contrast-induced nephropathy be considered one of the indications for the use of LOCM or IOCM, whereas in patients with normal renal function and no risk factors present, no advantage over the traditional HOCM has been shown [81].

Of late, interest has grown in a new nonionic, dimeric IOCM named iodixanol. Previously, extensive investigations performed in low-risk patients (patients without diabetes who had normal renal function) had shown no difference between the frequency of nephropathy associated with iodixanol and that associated with LOCM [31, 109, 110]. However, Chalmers and Jackson [111] subsequently published the first study to suggest that there was a reduced incidence of nephropathy with iodixanol. They investigated 124 consecutive patients with renal impairment (serum creatinine levels > 150 μmol/L) undergoing renal angiography, peripheral angiography, or both (half of whom had diabetes) and found that iodixanol was less than half as nephrotoxic as iohexol, a nonionic monomeric LOCM (a rise of > 10% in serum creatinine levels was seen in 15% of the iodixanol group vs 30% in the iohexol group; $p < 0.05$). A recent double-blind randomized controlled study of 129 patients by Aspelin et al. [81] confirmed this finding and reported that the likelihood of high-risk patients' developing contrast nephropathy appears to be significantly reduced by the use of an IOCM, as compared with an LOCM (odds were 11 times lower) [81]. However, the study was limited by the failure to control for volume of contrast agent administered.

Diuretics

It has previously been recommended that furosemide or mannitol administered in conjunction with a saline infusion offers better protection of renal function, but consistent results have not been obtained. Although mannitol has been shown to prevent ischemic renal failure and maintain GFR during renal hypoperfusion in animal models, it has not been shown to prevent acute renal failure in animal models with contrast-induced nephropathy [1].

Clinical trials have been similarly unconvincing. Anto et al. [12] claimed a protective effect of mannitol in an early study of 37 patients with chronic renal insufficiency who were hydrated before and after urography and were given 250 mL of 20% mannitol 1 hr after contrast administration, when compared with a group of 40 patients with a history of chronic renal insufficiency who received hydration alone. The incidence of contrast-induced nephropathy (defined as a 25% increase in serum creatinine levels) was found to be 22% in the treated group versus 70% in the group who received hydration alone. However, hydration protocols differed substantially between the two groups [12]. In the previously mentioned prospective study of Solomon et al. [22], simple fluid therapy was found to be significantly superior to fluid therapy plus either furosemide or mannitol. Indeed, an exacerbation of contrast-induced nephropathy (defined as an increased of > 0.5 mg/dL of serum creatinine levels) occurred with the concomitant use of furosemide. This deleterious effect was not found to be secondary to extracellular volume depletion, which was assessed by the patient's weight. In addition, hospitalization for all patients who developed contrast-induced nephropathy was increased by 4 days in those who received concomitant diuretic therapy.

Several other prospective randomized studies have suggested that the use of these drugs may paradoxically have a deleterious effect on renal function, especially in patients with diabetes. Weinstein et al. [112] found a worsening of renal function in eight patients with preexisting azotemia who were treated with furosemide and hydration versus a control group of 10 patients who did not have a deterioration in renal function and for whom hydration was left to the discretion of the referring clinician. Weisberg et al. [25] studied 50 patients, comparing fluid therapy against fluid therapy plus either dopamine, mannitol, or ANP, and found that no protective effect was offered by the addition of any of the previously mentioned agents; indeed, the incidence of nephropathy was increased by these agents in patients with diabetes. It has been reported that some uncontrolled clinical evidence indicates that temporary discontinuation of diuretics before contrast administration may be beneficial [113].

ANP

ANP, with or without saline, has been reported as reducing the incidence of contrast-induced nephropathy [114], by increasing GFR and glomerular hydrostatic pressure by dilating afferent arterioles and constricting efferent arterioles, while blocking tubular reabsorption of sodium and disrupting the tubuloglomerular feedback mechanism [113].

The Auriculin Anaritide Acute Renal Failure Study Group, a multicenter randomized double-blind placebo-controlled trial of anaritide (the synthetic form of ANP) in 504 critically ill patients with acute tubular necrosis, suggested improvements in dialysis-free survival in patients with oliguria [115]. Twenty-four-hour IV infusion of either anaritide at a rate of 0.2 μg/kg per minute or a placebo was administered, and the primary end point was dialysis-free survival for 21 days. The overall rate of dialysis-free survival did not improve with anaritide (47% dialysis-free survival rate in placebo group vs 43% in the anaritide group). Subgroup analysis of the 120 patients with oliguria (< 400 mL of urine output per day) showed a 27% dialysis-free survival rate versus 8% in the placebo group but showed a detrimental effect of anaritide in patients without oliguria (48% dialysis-free survival vs 59% in the placebo group). Although this study confirmed the fact that patients with acute tubular necrosis and oliguria have a worse clinical outcome, it was hoped that anaritide would be of use in this high-risk group. However, the subsequent definitive trial to assess safety and efficacy of anaritide in this

subgroup of patients with oliguria and acute renal failure did not confirm this result. Using the same regimen as outlined previously, Lewis et al. [116] assessed 222 patients with oliguric acute renal failure using end points of 21-day dialysis-free survival and 60-day dialysis and mortality rates. There was no statistically significant benefit to anaritide in these primary end points, but a significant drop in blood pressures was recorded in the ANP group, 95% of whom had a systolic blood pressure of less than 90 mm Hg during the study infusion ($p = 0.001$) versus 55% in the placebo group.

Kurnik et al. [117] studied 247 high-risk patients (renal impairment and diabetes mellitus in 50%) and showed the frequency of contrast-induced nephropathy to be higher in the anaritide group (23–25%) than in the placebo group (19%). Subgroup analysis showed no treatment benefit in patients with diabetes. Weisberg et al. [25] also found no additional protective benefit from treatment with ANP when compared with fluid hydration alone. ANP is thus no longer recommended for prophylaxis of contrast-induced nephropathy.

Calcium Channel Blockers

The role of calcium as a mediator of contrast-induced nephropathy, thought to be related to its positive effect on hemodynamics and their cytoprotective influence on renal cells, was first investigated in a clinical setting by Neumayer et al. [118] in a randomized double-blind study of nitrendipine. Administered before contrast application in a variety of studies including excretory urography and renal arteriography, nitrendipine attenuated contrast-induced decline in GFR, with a return to baseline after 48 hr. In contrast, there was a 26% reduction in GFR in the control group. Similar results were found in another study, which, unfortunately, had only a short-term follow-up of 2 hr [119]. However, Solomon et al. [22] found no benefit from a single preprocedural dose of calcium channel blocker in their series of 78 patients with chronic renal impairment undergoing angiography.

Similarly, Khoury et al. [120] performed a prospective randomized clinical trial of nifedipine but found that a 10-mg dose administered 1 hr before imaging made no statistically significant difference in renal function between the 42 treated patients and the 43 controls. However, mean increases in serum creatinine levels were very low in both groups (< 0.1 mg/dL). Despite this low increase, the authors concluded that prophylactic nifedipine is not clinically beneficial and should not be routinely administered for prophylaxis of contrast nephropathy.

More recently, the findings of a clinical trial of 27 patients (15 patients with diabetes and 12 without diabetes) with normal to moderately reduced renal function, who underwent femoral angiography with an LOCM (iohexol) and hydration before the examination, showed no major protective effect to be gained from felodipine (10 mg orally 3–4 hr before angiography). Indeed, there was a significant rise in serum creatinine levels in the felodipine group, which was not seen in the placebo group ($p < 0.05$) [121].

In spite of these negative results, Duan et al. [122] recently reported that amlodipine prevented renal injuries induced by diatrizoate in rats, and Wang et al. [123] found diltiazem (10 mg/kg injection intraperitoneally 30 min before contrast injection) also prevented the risk of increased serum creatinine levels observed with the administration of 6 mL of diatrizoate in five rat models. Given the lack of resoundingly positive results in human trials, calcium channel blockers have failed to gain wide use as a prophylactic tool to date.

Adenosine Antagonists

Adenosine, a potent vasoconstrictive agent, has been implicated as a mediator in tubuloglomerular feedback, a mechanism that may have a role in the pathogenesis of contrast-induced nephrotoxicity. Experimental studies of acute renal failure in different animal models reveal a nephroprotective effect of adenosine antagonism [54–57]. Theophylline acts as a nonspecific adenosine receptor antagonist and may be given as an IV bolus of 2.5–5 mg/kg of body weight before administration of contrast agent or orally for three consecutive days before contrast injection [124, 125]. The use of theophylline as a prophylactic agent for contrast-induced nephropathy was first assessed by Erley et al. [124]. Forty-five patients were given IV theophylline or a placebo; 4-hr inulin clearance and 48-hr creatinine clearance were stable or minimally reduced in the theophylline group but diminished in the placebo group.

More recently, a study of 100 patients with serum creatinine levels of 1.3 mg/dL or greater and who received either 200 mg of IV theophylline or a placebo 30 min before administration of 100 mL or more of an LOCM arterially (72%) or IV (28%) showed the benefit of pretreatment with the adenosine antagonist [126]. The incidences of contrast-induced nephropathy (defined as a serum creatinine level increase of at least 0.5 mg/dL in 48 hr) were significantly reduced in the theophylline group (4% vs 16%; $p = 0.046$) with minimal change in the mean serum creatinine levels, whereas the placebo group had a significant increase in 24-hr serum creatinine levels ($p = 0.006$). These results mirror those of the earlier work of Huber et al. [127] involving 78 patients in the ICU.

Kapoor et al. [128] confirmed these findings in a prospective study of oral theophylline (200 mg twice daily administered 24 hr before and for 48 hr after the procedure) in a group of 70 patients with diabetes mellitus undergoing coronary angiography. The control group again exhibited an increase in serum creatinine levels ($p = 0.003$) along with a decrease in GFR ($p = 0.008$) compared with the treated group. Contrast nephropathy (defined as ≥ 25% decrease in GFR) developed in 31% of the control group but developed in only one patient in the theophylline group.

A study of 58 low-risk patients (exclusion criteria included the following: serum creatinine levels >1.4 mg/dL, diabetes, congestive heart failure, hypertension, and multiple myeloma) undergoing contrast-enhanced radiographic procedures (all received an injection of 40 mL of an HOCM) confirmed the findings of Kapoor et al. [128]. When IV theophylline (165 mg) was compared with a similar volume of placebo (20 mL of saline), a significant decrease in GFR ($p = 0.001$) and increase in serum creatinine levels ($p < 0.001$) were again seen in the placebo group but prevented in the theophylline group. All changes in renal function were transient, returning to normal within 24 hr. This finding may reflect the normal prestudy renal function of the patient cohort but also calls into question the clinical significance of the findings.

Similarly, in a study of 93 patients, Katholi et al. [47] suggested that theophylline may have a protective effect. Patients with baseline creatinine levels of less than 2.0 mg/dL were randomized to receive oral theophylline (2.88 mg/kg twice daily for 2 days) or a placebo before the administration of an LOCM or HOCM. In the LOCM group (iopamidol), the authors found that theophylline prevented any decline in creatinine clearance, which was seen in the placebo-matched group (0% vs 18%); in the HOCM group (diatrizoate), creatinine clearance decreased by 42% in the placebo group but by

only 24% in the treated group. These findings may merely suggest that LOCM offers better protection than the HOCM and theophylline combined. An absence of significant changes in serum creatinine levels was seen in both treated and placebo groups; however, this lack of change brings into question the clinical relevance of the findings.

A subsequent trial by Erley et al. [129], which studied 64 patients with preexisting chronic renal insufficiency (serum creatinine levels > 1.5 mg/dL) showed no significant change in serum creatinine levels or creatinine clearance in either group (all patients received >100 mL of iopromide, an LOCM, and IV hydration before CT or peripheral angiography and were subsequently randomized to receive 840 mg of oral theophylline a day or a placebo). This finding suggests that LOCM use and hydration (which was not used in the first trial of Erley et al.) may be sufficient to prevent nephropathy and that the addition of theophylline did not result in a further benefit. However, the authors suggested that adenosine antagonists may have a role to play in cases in which sufficient hydration may not be possible, such as in congestive cardiac failure, in which there is concomitant decrease in renal blood flow. Prospective trials involving this subset of previously excluded patients have yet to be performed.

Several studies have shown no benefit of adenosine antagonism administered before a procedure. Abizaid et al. [130] performed a study involving 60 patients undergoing coronary angioplasty randomized to receive saline, dopamine, or aminophylline and found no differences among the three groups, and a study by Shammas et al. [131] of 26 patients receiving 200 mg of IV aminophylline found no appreciable differences when compared with the same number of matched control subjects. The study of Gandhi et al. [132] had a similar negative outcome, with no clinically beneficial effect from the use of theophylline.

In the wake of a lack of consensus in clinical studies, coupled with potential side effects of theophylline (such as a propensity to cause arrhythmias and convulsions) and the narrow therapeutic index of this drug, adenosine antagonism cannot yet be recommended for routine prophylactic use in the current clinical setting. A definitive multicenter prospective trial is warranted to confirm or deny the encouraging findings from earlier studies.

Dopamine Agonists

Dopamine is a potent vasodilator of the renal arteries. Hans et al. [133] used a dopamine infusion of 2.5 μg/kg per minute during and after angiographic procedures and reported that it provides protection against contrast-mediated renal dysfunction, despite the fact that they found only a small improvement in renal function, which was not sustained after day 1. The study was further limited by the small number of subjects (n = 60) and limited length of follow-up.

In addition, a more recent report failed to confirm the findings of Hans et al. [133], when it was found that dopamine, compared with IV saline, had a deleterious effect on the severity of renal failure and prolonged the course of contrast-induced acute renal failure [131]. Allaqaband et al. [102] found that fenoldopam offered no additional benefit over hydration with saline in patients with chronic renal insufficiency (baseline creatinine levels > 1.6 mg/dL or creatinine clearance < 60 mL/min) [114]. Similarly, Weisberg et al. [25] not only found an absence of benefit in treatment with dopamine but also observed that like diuretics, dopamine had a deleterious rather than a protective effect on renal function in patients with diabetes (incidence of contrast-induced nephropathy, defined as 25% increase in serum creatinine levels within 48 hr, was 83% in patients with diabetes receiving dopamine vs 0% in the diabetic group receiving a placebo).

Anecdotal evidence to the contrary, however, suggests that the selective dopamine type 1 receptor agonist, fenoldopam mesylate, may be useful in preventing contrast-induced nephropathy. It produces vasodilatation in vessels rich in dopamine type 1 receptors such as renal, mesenteric, and peripheral arteries but does not stimulate dopamine type 2 or adrenergic receptors, even at high doses. It is a potent relaxant of glomerular arterioles, preferentially acting on the efferent arterioles, and is six times more potent than dopamine in increasing renal blood flow [134]. Bakris et al. [135] showed that it prevented contrast-associated decreases in renal blood flow in volume-depleted dogs.

Chamsuddin et al. [134] found that an IV infusion of fenoldopam mesylate offered patients at high risk of developing contrast-associated nephropathy "a chance to avoid this complication." Twenty-nine high-risk patients (those with chronic kidney failure, renal artery stenosis, combined kidney and liver dysfunction, or congestive heart failure) had an IV infusion of 0.1 μg/kg per minute started 2 hr before the procedure and increased every 20 min in increments of 0.1 μg/kg per minute, according to the patient's blood pressure, until a rate of 0.5 μg/kg per minute was reached. This was maintained at the highest achieved dose during and for a minimum of 4 hr after the procedure. Twenty-four hours after the procedure, 16 of the 28 patients showed decreases in serum creatinine levels by an average of 0.55 mg/dL, nine showed no change, and three had increased levels. Six of the 29 patients could not be administered the maximal dose because of profound hypotension.

In a similar study, Kini et al. [136] reported a protective effect in patients with diabetes and impaired renal function who were undergoing coronary angiography. The studies of Kini et al. and Chamsuddin et al. [134] were retrospective; however, they had small numbers of patients and lacked a control group. A recent report from the more definitive Evaluation of Corlopam in Patients at Risk for Renal Failure: A Safety and Efficacy Trial has failed to corroborate these earlier findings. In a multicenter prospective randomized trial, 315 patients with creatinine clearances of less than 60 mL/min who were undergoing invasive cardiac procedures in 28 different centers were randomized to receive a regimen of fenoldopam and IV hydration or IV fluids alone. Contrast-induced-nephropathy occurred in 33.6% of those in the fenoldopam and IV fluids group versus 30.1% in the control group. Dopamine agonists are thus no longer recommended for contrast-induced nephropathy prophylaxis [137].

Endothelin Receptor Blockers

Oldroyd et al. [49] suggested that bosentan, an orally active endothelin antagonist, may attenuate the contrast-mediated reduction of renal function in the isolated perfused rat kidney and in a multiple-insult rat model with contrast-induced renal dysfunction. However, Katzberg [2], in his extensive review, raised numerous issues in relation to the study, namely the relevance of the multiple-insult rat model and isolated perfused kidney preparations to the clinical setting in terms of the exaggerated challenge to the kidney induced by a 5-day salt restriction, a very high-dose regimen of indomethacin, and the extremely high dose of contrast agent administered.

In addition, a recent prospective multicenter randomized trial has shown that endothelin-receptor antagonists actually exacerbate radiographic contrast-induced nephrotoxicity. Wang et al. [44] studied 158 patients with chronic renal insufficiency (mean creatinine level, 2.7 mg/L ± 1 mg/dL) undergoing cardiac angiography who were randomized to receive a mixed

endothelin A and B antagonist or a placebo. All patients were hydrated with 0.45% saline. The mean serum creatinine levels and the incidence of contrast nephrotoxicity (defined as an increase in serum creatinine levels of ≥ 0.5 mg/dL or a > 25% increase from baseline within 48 hr) were found to be increased in the treated group (p = 0.002; incidence of 56% in the treated group vs 29% in the placebo group). This negative effect was apparent for patients with and without diabetes [44].

Prostaglandins

A report on a pilot study of 117 patients receiving three separate doses of prostaglandin E_1 (alprostadil) or a placebo suggested that contrast-induced nephropathy was reduced in the prostaglandin group, but at higher doses, prostaglandin E_1 caused frequent hypotension and a higher rate of nephropathy [138].

More recently Koch et al. [139] performed a pilot study in 130 patients with renal impairment (defined as serum creatinine levels of ≥ 1.5 mg/dL) to assess the effectiveness and compatibility of prostaglandin E_1 in preventing contrast-induced renal dysfunction (analyzed using three separate definitions of a rise in serum creatinine levels: ≥ 0.5 mg/dL, ≥ 1.0 mg/dL, or ≥ 1.5 mg/dL, within 48 hr of contrast injection) at three different doses: 10, 20, and 40 ng/kg per minute of IV infusion over 6 hr, starting 1 hr before contrast injection, versus IV physiologic saline placebo. The authors found that in the placebo group, the mean rise in serum creatinine levels was significantly higher (0.72 mg/dL) than that in the three separate prostaglandin E_1 dosage groups (0.3 mg/dL in the 10 ng/kg per minute group, 0.12 mg/dL in the 20 ng/kg per minute group, and 0.28 mg/dL in the 40 ng/kg per minute group). None of the four groups showed a significant change in creatinine clearance, a phenomenon the authors attribute to the fact that GFR is known to be overestimated in patients with renal dysfunction as a result of active creatinine secretion in the tubules.

Although these results are promising, the study was limited by the small number of patients in each of the separate study groups and by the fact that the trial did not strictly control hydration status, type of contrast agent used (86% had nonionic and 11.5% had ionic contrast agents administered), mode of administration of contrast material, and volume of contrast material given (volumes ranged from 20 to 445 mL). In addition, six patients had serious adverse events that resulted in discontinuation of the prostaglandin infusion (arterial hypertension, arterial hypotension [m = 2], unstable angina, massive hematuria, and atrial tachycardia); an unspecified number of patients had nausea and vomiting, fatigue, and moderate skin symptoms; and a significant number of patients experienced a substantial drop in blood pressure during the IV infusion. The authors did not discuss these significant issues and concluded that prostaglandin E_1 may be used efficaciously and safely to prevent renal dysfunction in patients with preexisting impaired renal function. Further large-scale trials with stricter controls are required, particularly to address the safety concerns mentioned previously.

Preventive Hemodialysis or Hemofiltration

Removal of contrast media by hemodialysis after the procedure in patients with preexisting renal failure has been shown to have no effect on contrast-induced nephropathy and is unwarranted as a routine practice [140, 141]. Vogt et al. [142] evaluated prophylactic hemodialysis to see if the contrast agent could be efficiently removed, thus reducing the concentration to which the kidneys were exposed, but this procedure showed no beneficial effect compared with using saline hydration alone. In addition, patients undergoing hemodialysis were more likely to have a decline in renal function and require additional hemodialysis.

However, Marenzi et al. [143] recently published a paper investigating the use of hemofiltration in prophylaxis of contrast-induced nephropathy. They studied 114 consecutive patients with chronic renal failure (serum creatinine levels > 2 mg/dL) undergoing coronary interventions. Patients were randomly assigned to receive either hemofiltration in an ICU setting or isotonic saline hydration in a step-down unit. Serum creatinine level increases of greater than 25% from baseline were found to occur less frequently among patients in the hemofiltration group than among control patients (5% vs 50%, $p <$ 0.001). In addition, temporary renal-replacement therapy was required in 25% of the control group and in only 3% in the hemofiltration group. In-hospital events (52% vs 9%) and mortality rates (14% vs 2%) and cumulative 1-year mortality figures (30% vs 10%) were all higher in the control group than in the hemofiltration group.

Although Marenzi et al. [143] attribute most of the benefits to hemofiltration, they admit that the intensity of care received by those in the hemofiltration group was higher and that the infusion of heparin, received during hemofiltration, may also have been beneficial. They account for their superior results over hemodialysis by the fact that hemofiltration is associated with hemodynamic stability, preserving the circulating blood volume and preventing renal hypoperfusion. In contrast, hemodialysis can induce hypovolemia and may consequently worsen renal ischemic injury, delay recovery of renal function, and result in the need for prolonged treatment.

Although these results are extremely encouraging, the widespread use of hemofiltration is limited by its relatively high cost. It does, however, offer a very high-risk group of patients (those with serum creatinine levels > 4 mg/dL and undergoing multiple interventions requiring a larger volume of contrast agent than that used during simple diagnostic radiographic procedures) an effective preventive strategy, which, with the use of a more selective criterion (serum creatinine levels > 2 mg/dL), Marenzi et al. (143) believe would greatly increase cost-effectiveness. However, these results are not directly applicable to all high-risk patients who are exposed to contrast agents for simpler procedures, and although hemofiltration may prove useful in the coronary care setting, the relevance of hemofiltration as a prophylactic strategy in general radiology departments is questionable.

Summary and Recommendations

Controversy over precise definitions and their clinical relevance and wide variations in reported incidence rates should not obscure the fact that contrast-induced nephropathy is a significant source of morbidity and mortality rates in the hospital setting. The pathophysiology of this condition is complex and is thought likely to be multifactorial. Despite this, radiologists must be able to identify high-risk patients. Although only preexisting renal impairment and azotemia with diabetes mellitus have been definitively accepted as independent risk factors, we recommend that a full risk assessment be performed when possible. The introduction of questionnaires to be included with outpatient appointment cards may have the additional benefit of highlighting other relevant information such as history of anaphylaxis or pregnancy or treatment with metformin (an oral hypoglycemic used by patients with diabetes that may accumulate if renal function is impaired and may

predispose to biguanide-induced lactic acidosis [which has a 50% mortality rate]) [2].

Close cooperation with the referring clinician is essential, and protocols should be considered to help establish a standard assessment of risk (e.g., safety checklists used in MRI departments) and to institute preventive measures such as routine hydration and discontinuation of potentially nephrotoxic drugs whenever possible in all patients referred for particular contrast-enhanced radiology procedures.

General measures should include the following: the weighing of the risk–benefit ratio in all patients, encouraging aggressive hydration before and after the procedure, and the use of the minimal contrast dose possible. Specific prophylactic measures should be instituted in high-risk patients. The radiologist should strive to ensure that a gap of greater than 72 hr is maintained between contrast studies. Alternative diagnostic procedures such as MRI should always be considered when possible in patients considered to be at high risk, and LOCM or IOCM, which has been shown to be less nephrotoxic than HOCM, should be used if the procedure is deemed essential.

Although, to our knowledge, even IV fluid therapy has not been adequately compared with nonintervention, the weight of evidence and clinical experience suggest a protective effect, so we conclude it is reasonable to give fluid therapy before contrast administration. Despite the use of NAC as a prophylactic agent in many centers, like IV hydration, it has yet to be categorically and definitively confirmed to be of benefit. However, in light of the recent favorable meta-analysis and given its favorable side effect profile and cost-effectiveness, the use of NAC as a prophylactic agent in at-risk patients is probably justified, at least until more definitive large-scale clinical trials into its effectiveness are performed.

Conflicting reports exist as to the efficacy and safety of other pharmacologic interventions. Adenosine antagonists such as theophylline have shown inconsistent results, and, given their narrow therapeutic index, will require further rigorous trials before they can be recommended as prophylactic agents. Mitigating circumstances may include critically ill patients in the ICU or those unsuitable for adequate rehydration, but prospective trials involving sufficient numbers of these subsets of patients have yet to be performed. Recently, fenoldopam, a selective dopamine agonist, has been shown to be unsuitable as a prophylactic treatment. Similarly, insufficient data are available on the use of calcium channel blockers and prostaglandin E_1, and the role of hemofiltration in patients with chronic renal failure has yet to be confirmed. ANP, endothelin receptor blockers, and diuretics, particularly furosemide, should be avoided. The current suggested mainstays of prophylaxis against contrast-induced nephropathy are summarized in Appendix 3.

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APPENDIX 1. Reported Risk Factors for Contrast-Induced Nephropathy

Preexisting Renal Impairment

Diabetes Mellitus with Renal Impairment

Reduced Intravascular Volume

- Congestive cardiac failure
- Liver cirrhosis
- Nephrotic syndrome
- Diuretics, especially furosemide
- Abnormal fluid losses

Prolonged Hypotension

- Concomitant use of diuretic and angiotensin-converting enzyme inhibitor

Metabolic Disorders

- Diabetes mellitus
- Hyperuricemia
- Hypercholesterolemia
- Hypercalcemia

Contrast Media

- Large volumes
- High osmolarity
- Repeated injections within 72 hr

Multiple Myeloma

Nephrotoxic Drugs

- Nonsteroidal antiinflammatory drugs
- Aminoglycosides
- Amphotericin B
- Cyclosporin A
- Platinum-based drugs
- Sulfonamides

Advanced Age

Hypertension

Proteinuria

Sepsis

Atopic Allergy

Appendix 2 appears on the next page

APPENDIX 2. Proposed Radiology Department Preprocedural Appointment and Checklist

Dear Sir/Madam,

You are scheduled to undergo a _____ on the __/__/__. You are required to abstain from solid foods from 12 midnight of the morning of your examination, but are encouraged to continue to drink as much clear fluids as possible until 2 hours prior to your appointment. If you are on fluid restriction for any reason, please contact your referring doctor.

Please fill out the following questionnaire.

1. Have you ever suffered from an allergic reaction (e.g. to shellfish, insect bites etc)? ☐Yes ☐No

2. (If female): Is there any chance you may be pregnant? ☐Yes ☐No
Please state the date of your last menstrual period if applicable __/__/__

3. Do you suffer from diabetes? ☐Yes ☐No
If so, do you take Glucophage (Metformin) tablets? ☐Yes ☐No

4. Have you ever suffered from kidney disease? ☐Yes ☐No
(if yes, please specify)_____
_____

5. Do you suffer from any of the following:
Heart failure ☐Yes ☐No
High blood pressure ☐Yes ☐No
High cholesterol ☐Yes ☐No
Gout ☐Yes ☐No
Liver disease ☐Yes ☐No
Multiple myeloma ☐Yes ☐No

6. To the best of your knowledge, are you currently taking any of the following medications:
-Anti-inflammatory drugs ☐Yes ☐No
-Immunosuppressive drugs ☐Yes ☐No
-Antibiotics ☐Yes ☐No
-Antifungal drugs ☐Yes ☐No
(if yes to any of the above, please specify) _____
_____
_____

Please bring this appointment card with you on the day of your examination. If you answer yes to any of the above questions, or have any questions in regard to the above procedure, please contact your referring doctor, or the radiology department.

Thank you for your cooperation.

Appendix 3 appears on the next page

APPENDIX 3. Preprocedural Methods to Prevent Contrast-Induced Nephropathy

Discontinue Medications

Nonessential nephrotoxic medications (e.g., nonsteroidal antiinflammatory drugs) and diuretics should be discontinued before the procedure when possible, ideally 2–3 days beforehand

+

Contrast Medium

Low-osmolar contrast or nonionic isoosmolar contrast agent (e.g., iodixanol)

+

IV Fluids

0.9% sodium chloride or 150 mEq sodium bicarbonate in 1 L of 5% dextrose–water IV at 1 mL/kg per hour for 6–12 hr before the procedure; continue for 12–24 hr after the procedure

+

***N*-Acetylcysteine**

600 or 1,200 mg by mouth twice daily the day before and day of the procedure or 150 mg/kg IV over .5 hr or 50 mg/kg IV over 4 hr

+

Daily Urea and Electrolytes

Monitor creatinine levels before the procedure and daily for 48–72 hr; outpatients should have urea and electrolytes routinely checked 3–5 days after the procedure

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