Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies

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Abstract

WITH THE INCREASING USE OF CONTRAST MEDIA in diagnostic and interventional procedures, nephropathy induced by contrast media has become the third leading cause of hospital-acquired acute renal failure. It is also associated with a significant risk of morbidity and death. The current understanding of the pathogenesis indicates that contrast-medium nephropathy is caused by a combination of renal ischemia and direct toxic effects on renal tubular cells. Patients with pre-existing renal insufficiency, diabetes mellitus and congestive heart failure are at highest risk. Risk factors also include the type and amount of contrast medium administered. Therapeutic prevention strategies are being extensively investigated, but there is still no definitive answer. In this article, we review the current evidence on the causes, pathogenesis and clinical course of contrast-medium nephropathy as well as therapeutic approaches to its prevention evaluated in clinical trials.

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Nephropathy induced by contrast media is a significant yet underestimated problem in clinical practice. With the increasing use of contrast media in diagnostic and interventional procedures over the last 30 years, this form of nephropathy has become the third leading cause of hospital-acquired acute renal failure, accounting for 12% of all cases.[1] The risk of contrast-medium nephropathy continues to be considerable, despite the use of newer and less nephrotoxic contrast agents in high-risk patients in recent years.[2] Affected patients are at increased risk of morbidity and death. They may require short-term hemodialysis, which can extend their hospital stay and increase the risk of permanent impairment of renal function.[1–3] We review recent evidence on the incidence of and risk factors for contrast-medium nephropathy as well as the current understanding of its pathogenesis and the therapeutic approaches to its prevention that have been evaluated in clinical trials.

Definition

Contrast-medium nephropathy is usually defined as impairment of renal function occurring within 48 hours after administration of contrast media.[4–6] It is manifested by an absolute increase in the serum creatinine level of at least 44 μmol/L,[5,7–9] or by a relative increase of at least 25% over the baseline value[10,11] in the absence of another cause. Because creatinine levels typically peak 3–5 days after administration of contrast media,[1,3] this definition may overlook a large group of patients in whom nephropathy develops up to a week after administration of contrast media. However, older, more conservative definitions have a lower sensitivity because they require greater increases in the serum creatinine level.[12,13] The current definition, which requires smaller increases in serum creatinine, is therefore more sensitive for the diagnosis of contrast-medium nephropathy associated with clinically important adverse short- and long-term outcomes.[4,6,14]

Epidemiology and pathogenesis

The rate of contrast-medium nephropathy reported in studies that included patients with pre-existing renal dysfunction or diabetes mellitus in whom a standard hydration protocol was not administered is between 12% and 26%.[4,7,15–18] Lower rates (3.3%) have been reported among patients without these risk factors.[5]

Experimental studies suggest that contrast-medium nephropathy results from a combination of renal ischemia and direct toxic effects on renal tubular cells.

Renal hemodynamic changes

Early trials showed a transient increase in renal blood flow after injection of contrast medium that lasted up to 20 minutes followed by a more prolonged decrease in blood flow that lasted 20 minutes to hours.[19,20] Subsequent animal studies showed that contrast media were associated with epithelial cell necrosis, primarily in the thin ascending limb in the renal medulla. The extent of these histologic changes correlated with the magnitude of disturbance in rat renal function.[21]

The renal medulla is uniquely susceptible to ischemic injury, and contrast media may cause medullar hypoxia by shunting blood flow to the renal cortex.[22,23] It has been suggested that the development of contrast-medium nephropathy is affected by changes in renal hemodynamics because of the effects of the contrast medium on the action of many substances, including increased activity of renal vasoconstrictors (vasopressin, angiotensin II, dopamine-1, endothelin and adenosine) and decreased activity of renal vaso-

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dilators (nitric oxide and prostaglandins).[24–26] Other factors that may decrease renal blood flow include increased viscosity of contrast media[27] and increased erythrocyte aggregation induced by contrast media, which results in diminished oxygen delivery.[28] Regardless of the underlying cause, animal studies have shown that the decreased renal blood flow and decreased glomerular filtration rate after exposure to contrast media seems to be more prominent among dehydrated rats than among animals with normal fluid volume.[29]

Direct toxic effect on renal cells

Pathological changes induced by contrast medium (e.g., epithelial cell vacuolization, interstitial inflammation and cellular necrosis) suggest a direct toxic effect of contrast media on renal tubular epithelial cells.[30,31] Apoptosis is also involved as a result of cellular injury.[30] Contrast media have been found to reduce antioxidant enzyme activity in the rat kidney, and direct cytotoxic effects mediated by oxygen free radicals have been found in canine and rat models of contrast-medium nephropathy.[30–33]

Effect of osmolality

Experimental evidence has shown that hyperosmolar contrast media induce renal hemodynamic changes and have direct toxic effects on renal epithelial cells. Non-contrast hyperosmolar solutions, such as saline and mannitol, can cause renal vasoconstriction, which results in reductions in renal blood flow and the glomerular filtration rate, albeit of a lesser magnitude than reductions seen with contrast media.[34,35] These nonspecific effects of hyperosmolality could be caused by osmolar-driven solute diuresis with activation of tubuloglomerular feedback or an increase in tubular hydrostatic pressures, which may cause compression of the intrarenal microcirculation and a decreased glomerular filtration rate. In addition, in an in vitro model with a renal epithelial cell line, DNA fragmentation (a marker of apoptosis) was increased in cells exposed to hyperosmolar contrast media, and the degree of fragmentation was proportional to the osmolality of the contrast medium.[36] Thus, there is evidence of a direct cytotoxic effect of contrast media that is independent of hypoxia and may be related to hyperosmolality of the contrast agent. However, when the renal effects of iso-osmolar contrast media, which have the lowest osmolality, were compared with the effects of hypo- and hyperosmolar contrast agents, there was no reduction in renal abnormalities with the iso-osmolar agents.[37] A possible reason is the increased viscosity of the iso-osmolar agents. Iso-osmolar contrast media have been reported to cause more proximal tubular cell vacuolization, erythrocyte aggregation and cessation of blood flow in the renal microcirculation.[38]

Despite inconsistent results from experimental studies, clinical trials seem to show that hypo-osmolar contrast media are less nephrotoxic than hyperosmolar agents in high-risk patients. Pooled data from 25 randomized trials showed that the risk of contrast-mediuim nephropathy was greater with hyperosmolar contrast media than with hypo-osmolar agents and that this difference was mostly limited to patients with pre-existing renal disease.[39] Recently, it has been shown that iso-osmolar agents may be even less nephrotoxic than hypo-osmolar agents in such patients.[40]

Risk factors

Risk factors for contrast-medium nephropathy are related to patient characteristics and to the contrast medium used (Table 1).[4,5,39,41,42]

Patient-related factors

The most important patient-specific risk factors are pre-existing renal insufficiency and diabetes (Table 1). The risk of contrast-medium nephropathy is directly proportional to the baseline serum creatinine level and increases further when diabetic nephropathy is present.[43,44] Contrast-medium nephropathy developed in one-third of patients who underwent percutaneous coronary interventions and who had a baseline serum creatinine level of 177 μmol/L or greater.[43] The incidence of contrast-medium nephropathy among diabetic patients has been reported to be 5%–30%;[42,44] even among these high-risk patients, clinically significant nephropathy usually occurred in patients with underlying renal dysfunction.[5,44]

A history of congestive heart failure is an independent risk factor for contrast-medium nephropathy and contributes an even greater risk in patients with diabetes or renal disease,[5,42] probably because of the effect of low cardiac output on renal blood flow. Other predictors of con-

Table 1: Risk factors for contrast-medium nephropathy

Risk factor	Odds ratio (95% CI)
Patient-related	
Pre-existing renal dysfunction[5]	
Serum creatinine level:	
1.2–1.9 mg/dL (106–176 μmol/L)	2.42 (1.54–3.79)
2.0–2.9 mg/dL (177–264 μmol/L)	7.37 (4.78–11.39)
≥ 3.0 mg/dL (265 μmol/L)	12.82 (8.01–20.54)
Diabetes mellitus[4]	5.47 (1.40–21.32)
Age (1-yr increment)[5]	1.02 (1.01–1.03)
Congestive heart failure[5]	1.53 (1.21–2.10)
Hypertension[41]	1.20 (1.06–1.36)
Low effective circulatory volume[5]	1.19 (0.72–1.95)
Myocardial infarction[5]	1.85 (1.31–2.63)
Use of intra-aortic balloon pump[42]	1.94 (1.08–3.49)
Other	
Osmolality and content of contrast medium in patients with pre-existing renal dysfunction (low- v. high-osmolality)[39]	0.50 (0.36–0.68)
Volume of contrast medium (per 100 mL)[5]	1.12 (1.02–1.23)

Note: CI = confidence interval.

trast-medium nephropathy include the presence of hypertension,[41] increased age, acute myocardial infarction within 24 hours before administration of the contrast agent,[5] hemodynamic instability and use of an intra-aortic balloon pump during percutaneous coronary intervention.[5] Certain medications, including angiotensin-converting-enzyme (ACE) inhibitors and NSAIDs, have been implicated by their effects on regional renal hemodynamics. However, data on the risk of contrast-medium nephropathy associated with drug therapy are contradictory and have come mainly from animal studies and retrospective analyses.[45,46]

Box 1: Risk assessment for predicting contrast-medium nephropathy after percutaneous coronary intervention[52]

Risk factor	Integer score
Hypotension	5
Use of intra-aortic balloon pump	5
Congestive heart failure	5
Serum creatinine > 133 μmol/L	4
Age > 75 yr	4
Anemia	3
Diabetes mellitus	3
Volume of contrast medium	1 per 100 mL used
Risk categories	**Total score**
Low	≤ 5
Moderate	6–10
High	11–15
Very high	≥ 16

Other factors

Risk factors not related to the patient include the type and amount of contrast medium administered (Table 1). The use of hypo-osmolar or iso-osmolar contrast media has been found to be beneficial in reducing the incidence of contrast-medium nephropathy among high-risk patients but not among patients without risk factors.[39,40] Additional trials are needed to confirm that iso-osmolar contrast media are the least nephrotoxic in the clinical setting.

The volume of contrast medium administered correlates with the risk of nephropathy.[4,5,47] In a series of consecutive patients undergoing coronary angiography, each 100 mL of contrast medium administered was associated with a significant increase of 12% in the risk of nephropathy.[5] Adjustment of the volume to the patient's body weight and serum creatinine level has been found to minimize the risk.[48] Similarly, it has been shown that exceeding a patient-specific maximum volume of contrast medium (recommended to be 5 mL × [body weight (kilograms)/serum creatinine level (micromoles per litre) ÷ 88.4]) is associated with a 12-fold increase in risk of hemodialysis.[47] Therefore, the amount of contrast medium used should be kept to a minimum and not exceed patient-specific maximum doses.

Whether to use nonionic or ionic contrast agents is still inconclusive. In 2 large studies, the benefit of nonionic contrast media was limited to patients with pre-existing renal dysfunction,[49,50] whereas a third study showed no benefit of nonionic over ionic contrast agents in patients either with or without pre-existing renal dysfunction.[51]

Risk stratification

Mehran and colleagues[52] developed a simple scoring method that integrates 8 baseline clinical variables to assess the risk of contrast-medium nephropathy after percutaneous coronary intervention (Box 1). They found that contrast-medium nephropathy was strongly associated with an increased risk score: the incidence was 7.5% among patients with a low score and 57.3% among those with a high risk score. This assessment tool uses readily available information and is easily incorporated into routine clinical practice in the evaluation of patients who might undergo procedures involving contrast media.

Clinical presentation

The serum creatinine level begins to rise within 24 hours after administration of a contrast medium in 80% of patients in whom contrast-medium nephropathy develops. In patients with severe renal failure necessitating a prolonged hospital stay or dialysis, the serum creatinine level almost always increases within the first 24 hours,[53] typically peaking on the second or third day after administration of the contrast medium and returning to baseline values within 2 weeks. It has been shown that even transient rises in the serum creatinine level are associated with longer hospital stays.[17]

Although few patients with contrast-medium nephropathy require dialysis, these patients have poor short- and long-term survival (Table 2).[4,42,54] About half require tempo-

Table 2: Rates of hemodialysis and death after contrast-medium nephropathy reported in clinical trials

Study	No. of patients	Diagnostic procedure	Dialysis rate, %	Mortality after dialysis, %
McCullough et al[4]	3 695	Coronary angiography	0.5	37
Gruberg et al[42]	12 054	Coronary angiography	0.4	17
Levy et al[54]	16 248	Radiocontrast procedure	1.1	12

Note: CABG = coronary artery bypass grafting.

rary dialysis (< 1 year), whereas the remainder require long-term dialysis. The rate of death among patients requiring temporary or long-term dialysis is high (12%–37%).

Prevention

Modification of risk factors

When possible, the administration of contrast media should be delayed in patients with circulatory collapse or congestive heart failure until their hemodynamic status is corrected. Administration should be delayed for 24 hours after myocardial infarction. Repeated exposure should be delayed for 48 hours in patients without risk factors for contrast-medium nephropathy, and for 72 hours in those with diabetes mellitus or pre-existing renal dysfunction. If nephropathy develops, repeated exposure should be delayed until the patient's serum creatinine level has returned to baseline levels.[2,12,53] NSAIDs, diuretics (when feasible) and possibly ACE inhibitors should be discontinued 1–2 days before administration of contrast media.[53] Most importantly, the smallest possible amount of nonionic, hypo-osmolar or iso-osmolar contrast medium should be used in patients with risk factors.

Therapeutic approaches evaluated in clinical trials

Saline hydration and forced diuresis

A standardized saline hydration protocol has been proven effective in reducing the risk of contrast-medium nephropathy and should be used routinely (Table 3).[7,55–58] In a study of the effectiveness of saline, mannitol and furosemide in preventing contrast-medium nephropathy after cardiac angiography in patients with renal insufficiency, the incidence of nephropathy was significantly lower among patients who received saline alone (11%) than among those who received saline plus mannitol (28%) or saline plus furosemide (40%). It was also considerably lower than the incidence reported among patients with similar pre-existing renal diseases who did not receive hydration in a standardized fashion.[4,15–17] These results were confirmed by the Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) Study,[55] which found no benefit to forced diuresis with intravenous crystalloid, furosemide, mannitol or low-dose dopamine therapy over hydration alone in patients exposed to contrast media who were at risk for nephropathy. The lack of beneficial effects of

Table 3: Effectiveness of saline hydration or forced diuresis, or both, in preventing contrast-medium nephropathy reported in clinical trials

Trial	No. of patients	Baseline SCr level, mean (SD), µmol/L*	Intervention†	Rate of nephropathy, %‡	Superior intervention	Comments
Solomon et al[7]	78	186 (53)	• 0.45% saline 12 h before and after contrast exposure	11	Saline hydration (p = 0.02)	Rate of nephropathy with saline was lower than that previously reported among other patients with pre-existing renal disease who did not receive a standard hydration protocol
			• 25 g of mannitol 1 h before contrast exposure	28		
			• 80 mg of furosemide 30 min before contrast exposure	40		
PRINCE[55]	98	230 (80)	• 0.45% saline (150 mL/h)	31	None	High urine flow rate was associated with lower rate of nephropathy (OR 0.91, 95% CI 0.54–1.55)
		203 (71)	• Furosemide (1 mg/kg) + dopamine (3 µg/kg per min) + mannitol (12.5 g)	32		
		239 (88)	• Furosemide + dopamine	34		
PREPARED[56]	36	≥ 124	• 0.45% saline (75 mL/h) for 12 h before and after contrast exposure	After 48 h, mean SCr increased by 0.21 (SD 0.38)	None	Larger quantities of fluids were administered in the oral hydration arm
			• Oral hydration (1000 mL over 10 h) followed by 0.45% normal saline IV for 6 h before contrast exposure	After 48 h, mean SCr increased by 0.12 (SD 0.23)		
Mueller et al[57]	1620	80 (range 44–141)	• 0.45% sodium chloride plus 5% glucose	1	Isotonic saline (p = 0.04)	Marked benefit was evident for women, diabetic patients and patients given > 250 mL of contrast medium
			• Isotonic (0.9%) saline	2		
Merten et al[58]	119	≥ 97	• Sodium chloride infusion (154 mmol/L)	13.6	Sodium bicarbonate (p = 0.02)	A 7-h hydration protocol was used (OR 0.88, 95% CI 0.79–0.97)
			• Sodium bicarbonate infusion (154 mmol/L)	1.7		

Note: SCr = serum creatinine, SD = standard deviation, NS = not significant, OR = odds ratio, CI = confidence interval.
*Unless stated otherwise.
†All interventions were intravenous (IV) unless stated otherwise.
‡For studies that did not report rates of contrast-medium nephropathy, the mean change in serum creatinine level (µmol/L) in each treatment group is given.

mannitol and furosemide may be explained by their physiologic renal effects. Mannitol induces a process of active osmotic diuresis, which increases renal oxygen consumption and also acts as a potent renal vasoconstrictor. Furosemide-induced diuresis may result in hypovolemia, which may increase the risk of renal tubule injury induced by contrast media.[7]

Two recent prospective randomized studies evaluated different hydration protocols in patients undergoing procedures requiring contrast media (Table 3).[57,58] The first study showed that the incidence of nephropathy was significantly lower among patients given an isotonic saline solution than among those given a hypotonic saline solution (0.7% v. 2.0% respectively).[57] In the second trial, hydration with sodium bicarbonate was found to be significantly more effective than hydration with sodium chloride in preventing contrast-medium nephropathy (incidence of nephropathy 1.7% v. 13.6% respectively).[58] However, further studies are required to clarify the role of hydration with sodium bicarbonate in preventing such nephropathy.

Vasodilators

Fenoldopam: Fenoldopam mesylate is a selective dopamine-1 receptor agonist that produces systemic, peripheral and renal arterial vasodilatation. The drug exhibits many desirable renal effects that support its use for the prevention of contrast-medium nephropathy, including decreases in renal vascular resistance and increases in renal blood flow, glomerular filtration rate, and sodium and water excretion.[25] The benefit of fenoldopam for the prevention of contrast-medium nephropathy has been demonstrated in a dog model and in nonrandomized clinical studies.[25,59–61] In a small double-blind, randomized controlled pilot trial, fenoldopam plus normal saline was found to attenuate reductions in renal blood flow induced by contrast media; it was also associated with a lower incidence of contrast-medium nephropathy than was normal saline alone, although the difference between the 2 groups was not significant.[62] The benefit of fenoldopam was not validated in a large multicentre randomized placebo-controlled double-blind trial.[63] Also, because of multiple confounders in the studies that did evaluate fenoldopam, a definitive conclusion regarding the drug's ability to protect against contrast-medium nephropathy could not be reached (Table 4).

In 2 recent large studies comparing fenoldopam with *N*-acetylcysteine, treatment with fenoldopam either had a similar, nonsignificant effect as that of *N*-acetylcysteine[64] or was inferior to it.[65] Therefore, the routine use of fenoldopam cannot be recommended at the present time.

Low-dose dopamine: Low-dose dopamine has been used to maintain renal perfusion and function in patients with renal insufficiency who have circulatory or hemodynamic instability. However, studies evaluating low-dose dopamine (2–5 μg/kg per minute) for the prevention of contrast-medium nephropathy have shown conflicting results (Table 4).[66–69] These different results may be related to the simultaneous activation of the dopamine receptor type 2 (DA_2), which, in contrast to the DA_1 receptor, reduces renal blood flow and the glomerular filtration rate.[70]

Adenosine antagonists: Contrast media stimulate the intrarenal secretion of adenosine, which binds to the renal adenosine receptor and acts as a potent vasoconstrictor, reducing renal blood flow and increasing the generation of oxygen free radicals as it is metabolized to xanthine and hypoxanthine. Studies evaluating the adenosine antagonists (aminophylline and theophylline) have shown inconsistent results (Table 4),[69,71–73] and therefore these antagonists should not be routinely used for the prevention of contrast-medium nephropathy.

Other vasodilator therapies with limited clinical evidence: The calcium-channel antagonists verapamil and diltiazem have been found to attenuate the renal vasoconstrictor response after exposure to radiocontrast media.[74] However, when the efficacy of the dihydropyridine calcium-channel blockers felodipine, nitrendipine and nifedipine was evaluated, results were inconsistent.[75,76]

Endothelin-1, a potent endogenous vasoconstrictor, is thought to play a role in the development of contrast-medium nephropathy. However, the use of a mixed endothelin A and B antagonist (SB 290670) was associated with a significantly higher incidence of nephropathy than was placebo.[77]

Prostaglandin E_1 (PGE_1) has vasodilatory effects that may be beneficial in preventing contrast-medium nephropathy. In one study, 130 patients were randomly assigned to receive either placebo or 1 of 3 doses of PGE_1. All of the patients received 2 L of fluid before and after the contrast procedure. The increase in serum creatinine level was smaller in all of the 3 PGE_1 groups than in the placebo group, but the difference was significant only in the medium-dose PGE_1 group (20 ng/kg per minute).[78]

Antioxidants

N-*acetylcysteine:* This drug is inexpensive, well tolerated and devoid of significant side effects. It reduces renal damage by scavenging oxygen free radicals, generated as a result of toxic damage to renal tubules.[8] In a randomized placebo-controlled clinical trial, *N*-acetylcysteine significantly reduced urinary levels of 15-isoprostane $F2_t$, a specific marker of oxidative stress.[79] *N*-acetylcysteine may also have direct vasodilating effects on the kidneys through an increase in the biologic effects of nitric oxide, which is a potent and stable vasodilator contributing to improved renal hemodynamics.[79] In one study, oral administration of *N*-acetylcysteine plus standard saline hydration was compared with hydration alone in patients with chronic renal insufficiency (mean serum creatinine level 216 [standard deviation 116] μmol/L) undergoing coronary angiography with intravenous administration of 75 mL of a nonionic,

Table 4: Effectiveness of vasodilators in preventing contrast-medium nephropathy reported in clinical trials

Trial	No. of patients	Baseline SCr level, mean (SD), µmol/L*	Intervention	Rate of nephropathy, %†	Superior intervention	Comments
Fenoldopam						
Kini et al[60]	110	> 133	• Fenoldopam mesylate (0.1 µg/kg per min) • Historical controls	4.5 19	Fenoldopam	Case–control series; coronary interventions were associated with hypotension
Madyoon et al[61]	46	211 (88)	• Fenoldopam mesylate (0.1–0.5 µg/kg per min) • Conventional therapy	13 38	Fenoldopam	Retrospective study; hydration not specified
Tumlin et al[62]	51	177–442	• 0.45% saline IV • 1/2 normal saline + fenoldopam mesylate (0.1 µg/kg per min)	41 21	None	Dose and duration of fenoldopam infusion may not have been optimal; rate of nephropathy was secondary end point
CONTRAST[63]‡	315	Cr clearance < 60 mL/min	• Saline + placebo • 1/2 normal saline + fenoldopam mesylate (0.1 µg/kg per min)	30 34	None	Dose and duration of fenoldopam infusion may not have been optimal; nonstandard hydration protocol used
Low-dose dopamine						
Hans et al[66]	55	124–309	• Saline IV • Saline IV + dopamine (2.5 µg/kg)	After 24 h, mean SCr ↑ by 17.1 µmol/L After 24 h, mean SCr ↓ by 1.6 µmol/L	None after 48 h	Dopamine infusion showed benefit after 24 h and in patients whose baseline SCr level was ≥ 2 mg/dL (177 µmol/L). No significant difference after 48 h
Kapoor et al[67]	40	133 (27)	• Dopamine (2–5 µg/kg per min) • Control group (no dopamine)	0 50	Dopamine ($p < 0.05$)	
Gare et al[68]	66	106 (4)	• 0.45% saline IV • 0.45% saline IV + dopamine (5 µg/kg per min)	After 48 h, mean SCr ↑ by 11.5 (SD 5.3) µmol/L After 48 h, mean SCr ↑ by 18.6 (SD 6.2) µmol/L	None	Among patients with peripheral vascular disease, change in SCr level was significantly greater in dopamine group than in control group
Abizaid et al[69] (second phase of study)	72	230 (44)	• 0.45% saline IV • 0.45% saline IV + dopamine (2.5 µg/kg per min)	30 50	Trend toward worse outcome with dopamine ($p = 0.09$)	Significantly more patients in dopamine group than control group required hemodialysis
Aminophylline + theophylline						
Kappor et al[71]	70	106 (18)	• 0.9% saline (1 mL/kg per h (control) • 0.9% saline (1 mL/kg per h) + oral theophylline (200 mg twice daily)	20 0	Oral theophylline ($p = 0.017$)	> 25% decrease in GFR occurred more frequently in control than in theophylline group ($p = 0.004$)
Huber et al[72]	100	186 (80)	• 0.45% saline • 0.45% saline + aminophylline (200 mg IV)	4 16	Aminophylline ($p = 0.046$)	
Abizaid et al[69] (first phase of study)	60	168 (35)	• 0.45% normal saline • Dopamine (2.5 µg/kg per min) + saline hydration • Aminophylline (0.4 mg/kg per h) + saline hydration	30 50 35	None	
Erley et al[73]	80	168 (44)	• Theophylline orally (270 mg morning; 540 mg evening) • Placebo	6 3	None	

Note: SCr = serum creatinine, SD = standard deviation, GFR = glomerular filtration rate.
*Unless stated otherwise.
†For studies that did not report rates of contrast-medium nephropathy, the mean change in serum creatinine level (µmol/L) in each treatment group is given.
‡Odds ratio (95% confidence interval): 1.11 (0.79-1.57). Odds ratios for other studies were not reported.

hypo-osmolar contrast agent.[8] The incidence of contrast-medium nephropathy was significantly lower in the *N*-acetylcysteine group than in the control group. However, the results of this study are confounded by a higher than expected incidence of contrast-medium nephropathy in the control group (21%). This rate is considerably higher than the rate of 11% among patients receiving saline hydration alone in a study reported by Solomon and associates,[7] despite the fact that the latter study frequently used hyperosmolar, ionic contrast media and higher volumes of contrast agents. Subsequent trials of *N*-acetylcysteine in patients with chronic renal insufficiency have provided conflicting results.[9,64,80,81] A meta-analysis of the first 7 reported trials showed that, compared with peri-procedural hydration alone, administration of *N*-acetylcysteine plus hydration reduced the risk of contrast-medium nephropathy by 56% among patients with chronic renal insufficiency (odds ratio 0.44, 95% confidence interval 0.22–0.88, $p = 0.02$).[82] The authors of 2 other meta-analyses[83,84] stated that it was impossible to draw general conclusions about the benefit of *N*-acetylcysteine in preventing contrast-medium nephropathy because of inconsistent study designs of the analyzed trials. A systematic review showed that studies reporting negative results for *N*-acetylcysteine had enrolled patients at lower overall risk of contrast-medium nephropathy compared with studies reporting positive results (incidence of nephropathy 11% and 24.8% respectively).[85] Therefore, *N*-acetylcysteine may be of benefit mostly in high-risk patients. We performed a meta-analysis that showed an overall benefit of the drug, but only in patients with more severe renal dysfunction (serum creatinine level > 221 μmol/L) or when a nonstandard or incomplete hydration protocol was used[86] (Table 5). By contrast, in trials showing no effect of *N*-acetylcysteine, patients had had less severe renal insufficiency and a uniform 24-hour hydration protocol had been used (Table 6). In patients undergoing emergency diagnostic procedures, in whom a full hydration protocol is not possible, an abbreviated hydration regimen plus oral[90] or intravenous[91] administration of *N*-acetylcysteine was successful in reducing the rate of contrast-medium nephropathy.

The development of contrast-medium nephropathy seems to depend on the amount of contrast agent given and on the dose of *N*-acetylcysteine.[92] In one study *N*-acetylcysteine prevented nephropathy in patients receiving small amounts of contrast medium,[11] whereas in another it was efficient in patients receiving moderate to high volumes.[80] In another study, a double dose of *N*-acetylcysteine plus intravenous saline hydration administered before and after angiography in patients with chronic renal insufficiency significantly reduced the incidence of contrast-medium nephropathy compared with a single dose of *N*-acetylcysteine.[92]

Table 5: Summary of prospective studies of *N*-acetylcysteine (NAC) versus placebo for the prevention of contrast-medium nephropathy in patients undergoing elective diagnostic procedures in which a beneficial effect was shown

Study	No. of patients	NAC dose	Procedure	Baseline SCr level, mean (SD), μmol/L	Increase in SCr level used to define nephropathy	Rate of nephropathy, %	Odds ratio (95% CI)*
Diaz-Sandoval et al[10]	54	600 mg twice daily (1 dose before and 3 doses after the procedure)†	Coronary angiography	141 (4)	> 25%	NAC: 8 Placebo: 45% $p = 0.005$	0.21 (0.06–0.80)
Kay et al[87]	200	600 mg twice daily for 48 h†	Coronary angiography with or without angioplasty	124 (39)	> 25%	NAC: 4 Placebo: 12 $p = 0.03$	0.32 (0.10–0.96)
Shyu et al[9]	121	400 mg twice daily for 48 h	Coronary angioplasty	248 (71)	≥ 44 μmol/L	NAC: 3 Placebo: 25 $p < 0.001$	0.13 (0.08–0.20)
Tepel et al[8]	83	600 mg twice daily for 48 h	Diagnostic CT scanning	216 (116)	≥ 44 μmol/L	NAC: 2 Placebo: 21 $p = 0.01$	0.10 (0.02–0.90)
Miner et al[81]	180	2000 mg twice daily (total 2–3 doses)	Coronary angiography or angioplasty	132 (33)	≥ 25%	NAC: 10 Placebo: 22 $p = 0.04$	0.37 (0.14–0.93)
MacNeill et al[88]	43	600 mg twice daily for 48 h†	Coronary angiography	141 (35)	≥ 25%	NAC: 5 Placebo: 32 $p = 0.046$	0.11 (0.01–0.99)

Note: SCr = serum creatinine, SD = standard deviation, CI = confidence interval.
*Odds ratios are for NAC v. placebo with end point of contrast-medium nephropathy.
†24-hour hydration protocol not used.

Given the mixed results of *N*-acetylcysteine studies and the lack of evidence-based consensus, only a general recommendation for the use of the drug can be made at this time. It may be used to prevent contrast-medium nephropathy in high-risk patients and as an abbreviated oral or intravenous regimen in patients requiring emergency diagnostic procedures using contrast media. The role of acetylcysteine as an adjunct to full saline hydration in lower-risk patients with mild renal insufficiency appears to be more limited.

Ascorbic acid: A recent randomized trial showed that the use of ascorbic acid was associated with a significant reduction of 62% in the rate of contrast-medium nephropathy among patients with renal insufficiency undergoing coronary angiography with or without intervention.[93] Further prospective studies are needed to validate these preliminary results.

Hemofiltration and hemodialysis

Hemodialysis immediately after exposure to contrast media has not been shown to be effective in preventiing nephropathy in patients with pre-existing renal insufficiency, and it may even increase the risk of nephropathy.[94] In a higher-risk patient population (mean serum creatinine level 265 μmol/L), hemofiltration seems to have a protective effect, including significant reduction in in-hospital and 1-year mortality compared with routine hydration.[95] However, the expense and complexity of hemodialysis may prevent its general application in procedures that require the use of contrast media.

Conclusions and future directions

The increasing number of diagnostic and therapeutic procedures that require the use of contrast media makes the prevention of contrast-medium nephropathy an important goal. Unfortunately, no single pharmacologic compound has been found yet that consistently improves on results seen with hydration alone.

There are general guidelines for the management of patients undergoing procedures requiring contrast agents (Fig. 1) and for risk assessment of contrast-medium nephropathy (Table 1, Box 1). In high-risk patients, the total dose of the contrast agent should be kept to a minimum, and hypo-osmolar or iso-osmolar agents should be used. In addition, all patients should receive adequate hydration. The benefit of pharmacologic prevention appears to be limited. *N*-acetylcysteine may be used in high-risk patients and in patients in whom full saline hydration cannot be administered. Under special circumstances, when a diagnostic procedure requiring contrast media has to be used in very high-risk patients (patients in intensive care

Table 6: Summary of prospective studies of *N*-acetylcysteine (NAC) versus placebo for the prevention of contrast-medium nephropathy in patients undergoing elective diagnostic procedures in which a beneficial effect was not shown*

Study	No. of patients	NAC dose	Procedure	Baseline SCr level, mean (SD), μmol/L	Increase in SCr level used to define nephropathy	Rate of nephropathy, %†	Odds ratio (95% CI)‡
Boccalandro et al[80]	179	600 mg twice daily for 48 h	Coronary angiography with or without angioplasty	159 (53)	≥ 44 μmol/L	NAC: 13 Placebo: 12	1.14 (0.43–2.98)
Durham et al[89]	79	1200 mg 1 h before and 3 h after the procedure	Coronary angiography	194 (35)	≥ 44 μmol/L	NAC: 26 Placebo: 22	1.27 (0.40–4.03)
Briguori et al[11]	183	600 mg twice daily for 48 h	Coronary or peripheral angiography with or without angioplasty	133 (35)	≥ 0.25%	NAC: 7 Placebo: 11	0.95 (0.61–1.48)
Allaqaband et al[64]§	123	600 mg twice daily for 48 h	Coronary angiography with or without angioplasty	177 (53)	≥ 44 μmol/L	NAC: 18 Placebo: 15	1.23 (0.34–4.51)
Goldenberg et al[86]¶	80	600 mg 3 times daily for 48 h	Coronary angiography with or without angioplasty	177 (34)	≥ 44 μmol/L	NAC: 10 Placebo: 8	1.30 (0.27–6.21)

Note: Note: SCr = serum creatinine, SD = standard deviation, CI = confidence interval.
*All patients received 24-hour saline hydration protocol.
†Difference was not statistically significant.
‡Odds ratios are for NAC v. placebo with end point of contrast-medium nephropathy.
§One group of patients was randomly assigned to receive fenoldopam plus hydration.
¶Beneficial effect was observed only in patients with baseline SCr level of 221 μmol/L or greater.

units with more severe renal dysfunction), the use of hemofiltration has been shown to improve short- and long-term outcomes.

Future studies should address the issue of preventing nephropathy in patients undergoing diagnostic or therapeutic procedures that require the use of contrast media who have not received, or who are unable to receive, appropriate hydration before the procedure. In addition, with the conflicting results observed in *N*-acetylcysteine trials, an appropriately powered multicentre randomized clinical study should be designed to evaluate the drug's efficacy in preventing contrast-medium nephropathy.

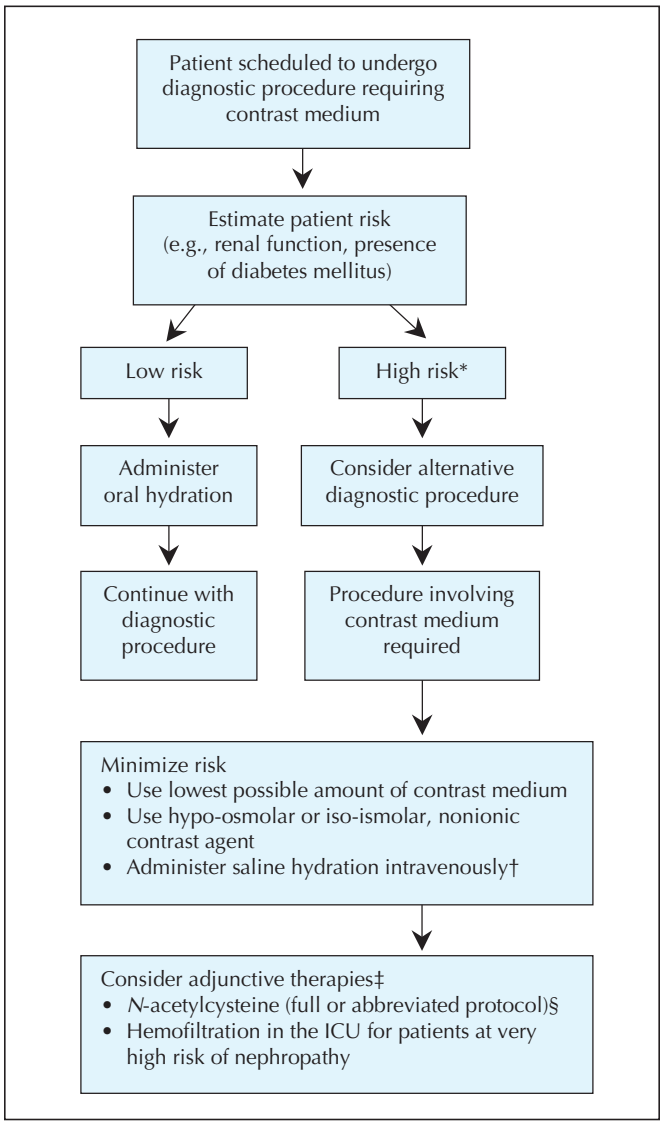

Fig. 1: Suggested management of patients scheduled to undergo diagnostic procedures involving use of a contrast medium. *Major risk factors are listed in Table 1. †A standard hydration protocol should include 45% saline administered intravenously at 1 mL/kg hourly, 12 hours before and after exposure to the contrast medium. ‡Large prospective studies are required to validate the efficacy of these therapies in specific subgroups of high-risk patients. §An abbreviated protocol with *N*-acetylcysteine may be required if full hydration is not feasible owing to severe unstable congestive heart failure or the need for an emergency procedure.

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