

iREVIEWS

STATE-OF-THE-ART PAPER

Nephrogenic Systemic Fibrosis

Review of 370 Biopsy-Confirmed Cases

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Discovery of an association between gadolinium-based contrast agents (GBCAs) and nephrogenic systemic fibrosis (NSF) has led to less use of GBCA-enhanced magnetic resonance imaging in dialysis patients and patients with severe renal failure at risk of NSF, and the virtual elimination of new cases of NSF. But shifting patients with renal failure to alternative imaging methods may subject patients to other risks (e.g., ionizing radiation or iodinated contrast). This review paper examines 370 NSF cases reported in 98 articles to analyze NSF risk factors. Eliminating multiple risk factors by limiting GBCA dose to a maximum of 0.1 mmol/kg, dialyzing patients undergoing dialysis quickly following GBCA administration, delaying GBCA in acute renal failure until after renal function returns or dialysis is initiated, and avoiding nonionic linear GBCA in patients with renal failure especially when there are proinflammatory conditions may substantially reduce the risk of NSF. (J Am Coll Cardiol Img 2011;4:1206–16) © 2011 by the American College of Cardiology Foundation

Nephrogenic systemic fibrosis (NSF) is a fibrosing condition involving skin, subcutaneous tissues, and sometimes internal organs that occurs only in patients with acute or severe chronic renal insufficiency. Discovery of an association with gadolinium-based contrast agents (GBCAs), especially at high doses (1), has led to hypotheses that GBCA could trigger this condition. Additional risk factors include dialysis (2), edema (3), hyperphosphatemia (4), epoetin use (5), and proinflammatory conditions (6). Food and Drug Administration (FDA) Black Box warnings and other regulatory actions have led to widespread screening of patients undergoing magnetic resonance imaging (MRI) for renal dysfunction and using less or no GBCA when the glomerular filtration rate (GFR) is estimated to be <30 ml/min. Since these warnings and regulatory actions have taken place (7,8), reports of NSF have decreased (Fig. 1), with virtually no new cases reported within the last 3 years (9,10).

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To better understand which patients with renal disease can safely undergo GBCA injection with minimal risk of NSF, we compiled data from 370 NSF cases detailed in 98 case reports of NSF and case series in which data on individual patients was available (1,6,11–106).

Clinical Features of NSF

NSF typically presents with skin thickening and hardening, especially in the lower extremities. The extent ranges from just a small patch of skin to extensive areas of the body. To date, this condition has universally spared the face. The thickened skin, sometimes described as “peau d’orange,” may acquire a cobblestone texture, dimpling, or a woody aspect, which is often accompanied by mild to moderate edema. The lesions may encompass joints. Joint contractures (n = 115) or limited range of motion (n = 23) were present in 138 of 190 patients for whom these data were available. Five additional patients reportedly had “stiffness” without contractures. This suggests that one-third of the patients had a mild form of NSF without contractures or limited range of motion.

Scleral plaque or injection was noted in 20 patients; otherwise, there was no facial involvement reported. Some of the imaging features reported included soft-tissue activity on bone scanning (n = 8), skin thickening on mammography (n = 4), dermal calcification (n = 9), and inflammatory changes on computed tomography (CT) scans (n = 14). In 16 patients, internal organ involvement was described.

NSF and GBCAs

In 76 of 98 articles, history of GBCA administration was investigated by the authors. Supplemental data were provided by the authors of 47 articles via e-mail communication so that data on GBCA exposure were available for 325 patients. In these patients, 298 (92%) were noted to have had GBCA injections prior to NSF symptom onset. The existence of NSF in patients without prior gadolinium exposure is one reason why the relationship of GBCA with NSF remains just an association, and GBCAs are not considered to be the proven cause of NSF. Gadolinium appears to be one of the

components that trigger NSF, but it may not be an exclusive or necessary component.

The time interval between GBCA injection and NSF was available for 196 patients. On average, NSF developed 96 days following GBCA, ranging from the same day to approximately 3 years. When intervals between GBCA exposure and symptom onset >1 year were excluded (i.e., no relationship for 9 patients with an interval >1 year), then the mean interval between GBCA exposure and symptom onset was 62 days. Data on the incidence of NSF in patients with renal failure who were exposed to GBCA are shown in Table 1. The wide range of incidence from 0% to 18% suggests that many variables affect NSF risk.

Age, Sex, and Race in Reported Cases of NSF

The distribution for 341 patients for which sex was available was approximately equally weighted between men (n = 181) and women (n = 160). For 359 patients with age reported, the mean age was 51 years (range, 8 to 87 years) (Fig. 1). There were no cases of NSF reported in neonates or toddlers, even though babies with immature kidneys and low GFR commonly receive high doses of GBCA, especially for imaging congenital heart disease. One possible reason is that the immune system at this age is not sufficiently developed to overreact to GBCA.

Reports of NSF in the aged (e.g., >70 years of age) are relatively infrequent, even though elderly patients have more severe renal disease and more per capita GBCA-enhanced MRIs. This potential discrepancy may be due to a less active immune system and reduced collagen synthesis in the elderly (107). Indeed, the oldest reported patient with NSF was only 87 years, in spite of many elderly older than 90 years with low GFR receiving high doses of GBCA.

In 173 patients, race was reported, including Caucasian (n = 96), black (n = 37), Hispanic (n = 7), Chinese (n = 7), Malay (n = 1), unspecified Asian (n = 1), Indian (n = 1), Vietnamese (n = 2), Japanese (n = 19), and Brazilian (n = 2). As expected, the majority of patients were Caucasian, reflecting a high use of GBCA-enhanced MRI in North America and Europe. Lower incidence of NSF in China in spite of a large population has been attributed to rare use of double- and triple-dose GBCA (108).

ABBREVIATIONS AND ACRONYMS

CVVH = continuous veno-venous hemofiltration

GBCA = gadolinium-based contrast agent

GFR = glomerular filtration rate

MRA = magnetic resonance angiography

MRI = magnetic resonance imaging

NSF = nephrogenic systemic fibrosis

PD = peritoneal dialysis

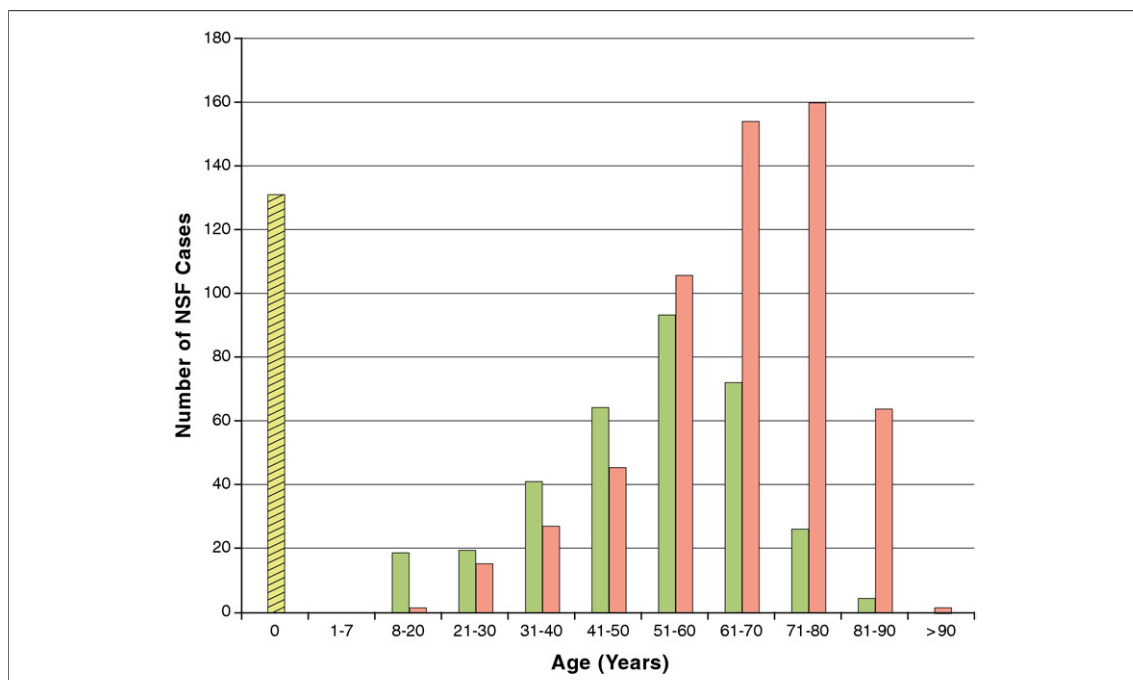


Figure 1. Incidence of NSF by Age

For 346 cases reported in the literature for which age is available, the number of patients with nephrogenic systemic fibrosis in each decade of age is shown in **green bars**. For comparison, the age distribution for patients undergoing high-dose magnetic resonance examinations with glomerular filtration rate <30 ml/min at Columbia College of Physicians and Surgeons, New York, New York, over 10 years is shown in **pink bars**. Note that the peak incidence of NSF occurs at 51 to 60 years of age, with no cases in patients <8 years of age. The number of infants <1 year (mean age 4.2 months) receiving high-dose gadolinium-based contrast agents (GBCAs) at Columbia is shown in a **yellow bar with diagonal stripes**. No NSF cases have been reported in infants in spite of their immature kidneys and a large number receiving high-dose GBCA. A dwindling incidence for age >70 years, even though there are many more at-risk patients (glomerular filtration rate <30 ml/min) receiving high doses of GBCA in elderly patients, was also noted.

Renal Function

All patients with NSF were reported to have renal dysfunction, and numerous authors emphasized the

Table 1. Incidence of NSF in Patients With Renal Failure Exposed to GBCA

Author (Ref. #)	Patient Cohort	No. of Patients With NSF	Incidence, %
Othersen (62)	261	4	1.5
Panda (113)	2,146 dialysis	6	0.28
Chen (69)	81 (GFR $<15^*$)	1	1.2
Rydahl (109)	102 (GFR $<15^*$)	18	18.0
Collidge (38)	421 dialysis	13	3.1
Shabana (106)	414 dialysis	12	2.9
Prince (1)†	265 dialysis	1	0.4
Reilly (119)	141 dialysis‡	0	0
Provenzale (125)	29 infected CRF	5	6.7
	305 uninfected CRF	2	0.26
Heinz-Peer (96)	367 dialysis	6	1.6

*Glomerular filtration rate (GFR) units: ml/min/1.73 m². †Note that this report made a distinction between patients on chronic hemodialysis at the time of gadolinium-based contrast agent (GBCA) administration (incidence of nephrogenic systemic fibrosis [NSF] 0.4%) and patients who started hemodialysis ≥ 2 days after GBCA administration due to acutely deteriorating renal function (incidence of NSF 19%). ‡Dialysis patients received solely gadoteridol. CRF = chronic renal failure.

highest risk of NSF for GFR <15 ml/min (i.e., chronic kidney disease stage 5 (109)). In 353 patients, there was sufficient detail reported to determine whether the patient around the time of developing NSF was on dialysis, including hemodialysis (n = 205), peritoneal dialysis (PD) (n = 37), both (n = 13), continuous veno-venous hemofiltration (CVVH) (n = 4), or unspecified (n = 37). Thus, 80% (296 of 370) of patients with NSF were on dialysis, indicating that it is a major risk factor. For 57 patients with NSF presumably not on dialysis, GFR was reported to range from 0 (anuric) to 40 ml/min, with a mean value of 15 ml/min. For 3 patients in whom estimated GFR was >30 ml/min, there was acute renal failure indicating that the true GFR was actually lower. Another patient with an estimated GFR greater than 30 ml/min had the GFR measured 1 month before GBCA injection.

Acute versus chronic renal failure. In 192 patients for whom data allowed discrimination between acute and chronic renal failure, 58 (30%) had acute or

acute deterioration of chronic renal failure. In the remaining 134 patients, there was sufficient detail to determine that the renal failure was chronic and stable. Acute renal failure has also been reported as an NSF risk factor, with an odds ratio of 13.4 (50). However, in these 58 patients with acutely deteriorating renal function at the time of GBCA administration, only 19 had contractions reported. Follow-up available for the 37 patients with NSF in acute renal failure showed that 2 had a complete resolution of NSF (5%) and 17 showed improvements (46%). This is consistent with the tendency for NSF to improve, with restoration of renal function that may occur when acute renal failure resolves. Thus, although acute renal failure increases NSF risk, the NSF clinical course may not be as debilitating.

One article looked at the difference in NSF risk with acute renal failure between injecting high-dose GBCA while serum creatinine level was rising (NSF incidence 19%) versus injecting after serum creatinine level had peaked (no cases of NSF in 41 patients) or after regular hemodialysis was started (no cases of NSF in 32 patients) (1). This suggests that NSF risk can be substantially reduced in patients with acute renal failure by either dialyzing shortly after GBCA injection or by delaying GBCA-enhanced MRI until after serum creatinine level has peaked and the renal failure is beginning to resolve.

Timely effective dialysis. Although 296 patients were on dialysis at the time of developing NSF, several factors may have reduced dialysis effectiveness in patients who developed NSF. In a disproportionately large number of cases, PD ($n = 37$) or CVVH ($n = 4$) was used; these methods of dialysis are known to be less effective at rapidly removing GBCA compared with hemodialysis (110,111). In 49 patients, it was specifically reported that GBCA-enhanced abdominal magnetic resonance angiography (MRA) was performed, which can assess for renal artery stenosis as the cause of renal failure before initiation of dialysis. When dialysis is initiated, the first sessions are lower intensity so that the patient can acclimate to the stress of hemodialysis. In addition, for patients awaiting initiation of dialysis, the interval between GBCA exposure for MRA and first dialysis may have been longer than the 2-day interval between sessions for patients on chronic dialysis. In an additional 7 patients, GBCA-enhanced MRA was used in patients undergoing chronic dialysis to evaluate dialysis fistulae. Patients undergoing dialysis with mal-

functioning fistulae may not undergo effective dialysis either before or following their GBCA-enhanced MRA.

For the 56 patients in whom the interval between GBCA administration and dialysis could be determined, dialysis was performed the same day in 6 patients, 1 day later in 13 patients, 2 days later in 9 patients, and ≥ 3 days later in 28 patients. This suggests that the overwhelming majority of patients on dialysis with NSF may have had a delay between GBCA and receiving dialysis, may have used PD or CVVH, were just beginning dialysis, or may have had poor-quality dialysis due to reduced fistula function. For 7 of the patients dialyzed within 2 days of GBCA exposure, the authors specifically noted that it was low-intensity dialysis, which could not be expected to remove as much gadolinium as standard hemodialysis (39,112,113). These data support the hypothesis that a single prompt, high-quality hemodialysis reduces NSF risk, perhaps on the order of 20-fold.

Kidney transplantation. Seventy-nine of 370 patients (21%) were noted to have a renal transplant around the time of the GBCA injection. In 36 of these 79 patients (46%), there was history of failing/failed renal transplant. Although it was not always possible to tell the reason for the MR examination, it appears that in most of these cases, GBCA was being injected for an MRA of the renal transplant artery to determine if there was a correctable renal transplant artery stenosis.

Liver disease. Although liver disease and liver transplantation have been singled out in regulatory warnings for extra caution, liver disease was actually noted in only 26 patients. Furthermore, a review by Mazhar et al. (114) showed that liver disease conferred no additional NSF risk beyond the risk related to the underlying renal dysfunction.

GBCA Dose

Several dose-reporting errors were corrected in the correspondence with authors. In the 248 cases for which data on GBCA dose were available or could be estimated from the exam type, 30 patients (12%) appeared to have received a standard dose of GBCA (0.1 mmol/kg) in the MRI exam most immediately preceding development of NSF, and 218 patients (88%) received greater than a standard dose, also known as high dose. The mean total dose was estimated to be 41 ml—assuming that 0.1 mmol/kg is 15 ml and that patients undergoing

Table 2. Effect of GBCA Dose on Risk of NSF in Case-Controlled Studies

Author (Ref. #)	No. of Controls	No. of Patients With NSF	GBCA Dose in Controls	GBCA Dose in Patients With NSF	p Value
Kallen (63)	14	13	20 ml	80 ml	0.01
Marckmann (115)	19	19	0.34 mmol/kg	0.44 mmol/kg	0.05
Collidge (38)	408	13	30 ml (0.23 mmol/kg)	45 ml (0.39 mmol/kg)	0.008

Abbreviations as in Table 1.

MRI had a standard dose, whereas patients undergoing MRA or using GBCA to replace iodinated contrast for angiography had a double dose. One article reported no cases of NSF in 63,597 single-dose gadodiamide administrations (without screening for renal function) but 15 cases of NSF following 8,997 high-dose GBCA administrations (1). Similarly, Broome et al. (112) described 12 cases of NSF in 210 patients undergoing dialysis receiving high-dose gadodiamide but no cases of NSF in 94 patients undergoing dialysis receiving single-dose gadodiamide. This yielded an odds ratio of 12:1 for high-dose GBCA causing NSF, indicating that the risk of NSF can be reduced 12-fold simply by using a standard dose of 0.1 mmol/kg. Additional data on the increased NSF risk with higher doses of GBCA from case-controlled studies (38,63,115) are listed in Table 2.

Although limiting the dose of GBCA to a standard dose of 0.1 mmol/kg reduced NSF risk by at least an order of magnitude, there have been reports of NSF developing after exams being repeated with a second injection due to nondiagnostic results with a poorly timed or extravasated first injection (1). Thus, it is also necessary that GBCA-enhanced MRI be performed particularly carefully in these patients so that diagnostic images are obtained and the patient does not require a repeat examination. Part of dose reduction includes having the best technologists and nurses performing the examinations on the best possible equipment for at-risk patients to mini-

mize the need for repeat injections. Moreover, MRA exams in the past used a high dose to make up for equipment limitations. With state of the art equipment, MRA is now possible with standard doses or less (116). FDA approval of gadofosveset, a high-relaxivity blood pool contrast agent, also allows diagnostic MRA with low doses even on older equipment.

Type of GBCA

Only 62 articles indicated the most likely type of GBCA to which 231 patients were exposed. One issue was a failure to keep accurate patients records concerning GBCA administration before discovery of the NSF association with GBCA such that the type of GBCA had to be inferred from purchasing or formulary records. Another issue is related to confusion about the GBCA names, which resulted in errata in at least 1 article (117). We also were able to make several corrections after author correspondence. Yet another issue pointed out by many authors was the uncertainty about patient exposures outside of the authors' institution.

When information on type of GBCA was provided, gadodiamide (n = 182), gadopentetate dimeglumine (n = 26), gadoversetamide (n = 5), gadobutrol (n = 3), and multiple agents (n = 15) were described; however, the accuracy and completeness of these data were sometimes questioned (1). The reports involving gadobutrol are controversial (118). The large number of cases with nonionic agents (gadodiamide and gadoversetamide) (Table 3), which tend to have lower in vitro stability compared with the ionic (gadopentetate dimeglumine, gadoxetate, gadofosveset, and gadobenate) and macrocyclic (gadoteridol, gadobutrol) agents, has led to hypotheses that lower chelate stability may contribute to greater NSF risk (119,120,121). However, this does not necessarily translate into greater overall risk for the individual patient because nonionic contrast agents tend to have fewer serious allergic-type adverse events (122,123) and fewer deaths (124).

Table 3. Comparison of NSF Risk With Gadodiamide (Nonionic) and Gadopentetate Dimeglumine (Ionic)

Author (Ref. #)	Year	Patient Population	NSF Cases With	
			Gd:DTPA	Gadodiamide
Prince (1)	2008	High dose; eGFR* <30†	0/87	12/411
Wertman (120)	2008	Unscreened	4/135,347	32/82,260‡
Broome (121)	2008	Worldwide NSF reports	8	157

*eGFR = estimated glomerular filtration rate calculated from serum creatinine level, age, race, and sex.
†GFR units: ml/min/1.73 m². ‡The odds ratio was 13.2 times greater for the risk with gadodiamide compared with gadopentetate dimeglumine (Gd:DTPA).
Abbreviations as in Table 1.

Type of MRI Exam

MRI exam type was reported for 192 patients, including 98 (51%) undergoing MRA, which likely reflects the common use of high doses for this exam (Table 4). Abdominal MRI (n = 36 [19%]), including liver and MR cholangiopancreatography, was the second most common exam type, which also likely reflects the tendency to use high doses for liver MRI before 2008. Interestingly, there are only 3 cases of cardiac MRI reported to be temporally correlated with developing NSF in spite of the common use of double-dose GBCA and high incidence of renal disease in cardiac MRI patients.

Proinflammatory Events

For 147 patients, it was possible to determine if there was a “proinflammatory event” at the time of GBCA injection, including recent major surgery (n = 81), acute thrombosis (n = 58), infection (n = 44), myocardial infarction (n = 2), antiphospholipid syndrome (n = 12), and active systemic lupus erythematosus (n = 15). Provenzale (125) noted that infection increased the risk of NSF in patients undergoing dialysis by 25-fold.

Epoetin

Epoetin is commonly given to patients with renal failure to boost hematocrit. Because epoetin is known to be proinflammatory, the possibility that it represents a contributing risk factor has been suggested by several authors (5,117). Epoetin acts through stimulation of the bone marrow; however, this stimulation is not specific to red cell creation. Other bone marrow cell production is also enhanced, including circulating free fibrocytes, which are implicated in the pathogenesis of NSF. In 82 patients for whom details on their medications were described, 66 (80%) were reported to be taking epoetin, including at least 7 patients on high doses.

Acidosis

Acidosis has been a suspected risk factor since the initial report by Grobner (23) of 5 patients who all had acidosis at the time of GBCA injection. In 43 patients, data on either blood gas results near the time of GBCA administration or bicarbonate allowed for an assessment of acidosis. Twenty-three patients (53%) were noted to be acidotic. This

acidosis is believed to be a risk factor for transmetallation because the extra positively charged protons presenting at lower pH compete with gadolinium-binding sites on the chelator, weakening the strength of the gadolinium-chelate bond. Association of acidosis with NSF has also been reported by others (56,126).

Hyperphosphatemia

Elevated serum phosphorus is common in patients with renal failure, and the mean serum phosphorus was 6.8 mg/dl (2.3 mmol/l) (normal 2.5 to 4.5 mg/dl [0.8 to 1.5 mmol/l]) for the 86 patients for whom data were available. Hyperphosphatemia presumably increases the risk of phosphate binding and precipitation of gadolinium when it is transiently released from the chelator, thereby preventing reassociation of gadolinium with the chelator. The experimental work of Frenzel et al. (4) has shown that the conditional stability of the nonionic linear GBCAs is further reduced with significantly increased (100-fold) release of gadolinium in plasma at pH 7.4 when 10 mmol/l phosphate was added to mimic the “milieu intérieur” of the chronic renal failure state. This resulted in a 75% increase in gadolinium release during the experiment compared with normal serum. The addition of phosphate in the same experiment with ionic linear chelates resulted in some increase in initial gadolinium release rate, but overall release was not increased over the 15 days of the study. There was no effect for macrocyclic GBCAs, which had no measurable release of gadolinium.

Table 4. Types of GBCA Enhanced Examination Preceding NSF

GBCA Exam Type	No. of Patients
MRA	98
MRI abdomen	36
MRI head	14
X-ray angiogram	13
MRI extremities	8
MRI unspecified	7
MRI pelvis	6
MRI spine	5
Cardiac	3
MRI neck	2

MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; other abbreviations as in Table 1.

Outcomes

Most of the information relating to the severity of the disease was subjective. For 254 patients for whom follow-up data were available, 55 experienced different degrees of NSF symptom improvement and cure was noted in 6 patients. Partial ($n = 8$) or complete ($n = 3$) improvement following restoration of renal function occurred in 11 cases. One patient with NSF was reported to have substantial improvement after renal transplant and again got worse after rejection (68). The clinical course was stable in 65 patients. Death was noted in 71 patients but was attributed to NSF in only 3 cases. Other causes of death included cardiopulmonary disease ($n = 20$), infections ($n = 7$), general anesthesia ($n = 1$), systemic lupus erythematosus ($n = 1$), lymphoma ($n = 1$), renal cell carcinoma ($n = 1$), myeloma ($n = 1$), toxic megacolon ($n = 1$), mesenteric ischemia ($n = 1$), severe stroke ($n = 1$), multiorgan involvement ($n = 2$), sudden death ($n = 1$), and unknown ($n = 30$). In 26 patients, the symptoms were progressive, and the authors only mentioned “alive” without further details for another 31 patients.

Screening to Identify Patients at Risk

Because 80% of patients with NSF were on dialysis, this is the most important risk factor for screening to identify at-risk patients. Renal transplant was present in 21% of patients with NSF, indicating

that this is another important risk factor. For all inpatients, existing serum creatinine data should be checked to identify patients with GFR lower than 30 ml/min. Serum creatinine level should also be checked in outpatients when severe renal impairment is discovered in the MR patient safety questionnaire.

Discussion and Conclusion

The surveys conducted in this paper suggest that many high-MR-volume institutions have had no recent NSF cases (1). In addition, changes in GBCA use since the association between NSF and GBCA was reported in 2006 have virtually eliminated new cases reported to the FDA (9), European Medicines Agency, and manufacturers. The data compiled in this review of 370 reported cases suggest that reductions in risk may be attained with each of the following: 1) avoiding high doses of GBCA (>0.1 mmol/kg); 2) avoiding nonionic linear chelates in patients undergoing dialysis and patients with GFR <30 ml/min, especially in the setting of proinflammatory conditions; 3) dialyzing quickly after GBCA administration for patients already on dialysis; and 4) avoiding GBCA in acute renal failure, especially while serum creatinine level is rising.

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Key Words: adverse event ■
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