No Incidence of Nephrogenic Systemic Fibrosis after Gadobenate Dimeglumine Administration in Patients Undergoing Dialysis or Those with Severe Chronic Kidney Disease[1]

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Purpose: To determine the incidence of nephrogenic systemic fibrosis (NSF) in patients with severe chronic kidney disease (CKD) who underwent a uniform protocol for contrast material–enhanced magnetic resonance (MR) imaging with a gadolinium-based contrast agent (GBCA).

Materials and Methods: This retrospective, single-center, institutional review board–approved, HIPAA-compliant study included 3819 patients with severe (stage 4 or 5) CKD who underwent gadobenate dimeglumine–enhanced MR imaging as part of a preoperative evaluation for potential renal transplantation from January 2008 to February 2014. After undergoing contrast-enhanced MR imaging, patients were assessed for NSF by means of clinical follow-up, including a full integumentary examination, with a minimum of 6 months between administration of the GBCA and clinical skin examination. Suspicious skin lesions were sampled with deep punch biopsy, and results of pathologic examination were reviewed and categorized. In addition, a search of the institution's pathology database during the time of the study was performed to identify any additional patients with NSF. The proportion of subjects who developed NSF after the administration of gadobenate dimeglumine was calculated, and Clopper-Pearson 95% confidence intervals were determined by using binomial proportions.

Results: The average length of follow-up for the patient population was 501 days (range, 186–2121 days). A total of 219 biopsies were performed, and none of the 3819 patients developed NSF after administration of gadobenate dimeglumine, resulting in a proportion of zero; the exact upper bound of 95% confidence interval was 0.000965 (0.0965%).

Conclusion: None of the 3819 patients with severe CKD developed NSF after undergoing gadobenate dimeglumine–enhanced MR imaging, which suggests that this GBCA may be safely administered in patients with severe CKD, with an immeasurable risk for the subsequent development of NSF.

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Nephrogenic systemic fibrosis (NSF) is a fibrosing disease of the skin and other soft tissues that is found in patients with advanced kidney disease. The histopathologic findings of NSF were first described in 2001 by Cowper et al (1), with historical first incidence noted to have occurred in 1997. In 2006, Grobner et al (2) and Thomsen et al (3) noted the correlation between NSF and previous magnetic resonance (MR) examination with a gadolinium-based contrast agent (GBCA). The first GBCA was introduced in 1987, 10 years before NSF was first diagnosed. It is presumed that the increasing use of contrast material–enhanced MR imaging, particularly for MR angiography, led to sufficient overall population exposure in at-risk patients and, consequently, to the clinical appearance of NSF (4).

A global NSF registry (5) has collected information regarding a total of 387 affected patients, with the incidence of NSF largely restricted to years 2000 to 2010. Most cases of NSF have been linked to the use of one of three different GBCAs (6,7) and have also been associated with higher doses of these agents as compared with a single dose at a level recommended for contrast-enhanced MR imaging (8,9). There is little evidence to show risk of NSF in patients with stage 3 or higher kidney function (10), with most patients with NSF found to have been dependent on dialysis at the time of GBCA exposure (11,12). No cure for NSF is yet known, and the role of hemodialysis after GBCA exposure remains unproven, although the procedure is recommended (9).

In 2006, the U.S. Food and Drug Administration (FDA) announced an indiscriminate warning against the use of GBCAs in patients with kidney disease. In 2010, the FDA updated the warning to differentiate three of the agents found to be associated with NSF, stating that these GBCAs should never be used in patients with advanced acute or chronic kidney disease (CKD). The FDA further recommended that all other agents be used with caution in patients with kidney disease but did not give specific instruction on methodology (13).

It has been presumed that the three agents most associated with NSF are chemically less stable than other ionic linear or macrocyclic agents with higher chemical chelate stability, leaving the gadolinium species more available for transmetallation (14). The common elimination pathway for GBCAs is through glomerular filtration. The role of alternative pathway elimination—liver uptake and bile excretion—noted with two of the linear agents (15) may also be protective. The American College of Radiology, in parallel with the FDA, has developed a risk stratification system for the different GBCAs (16), classifying the three agents most associated with NSF as group I. Other agents stratified as lower risk are classified as group II (linear agent, not associated with NSF, or macrocyclic agent). GBCAs with limited data regarding NSF or that have only recently appeared on the market are classified as group III.

Previous reports have shown an NSF incidence of 3%–5% in patients who are undergoing hemodialysis or peritoneal dialysis (patients who undergo dialysis have the highest risk for NSF) and have been exposed to a group I GBCA (9,17), although these reports do not address patients with a requirement for next dialysis within 24 hours. The current observed decrease in NSF incidence (18) presumably results from changed practices influenced by warnings and guidelines, including those issued by the FDA and the American College of Radiology. It was shown in a study of data from the Veterans Affairs Health Care System that practice patterns have changed and that contrast-enhanced MR imaging has been avoided in patients suspected of having kidney disease (19). In a subset of university medical center practices, in which NSF had been reported previously, there has been subsequent published evidence of diminished incidence of NSF despite continued use of certain GBCAs for contrast-enhanced MR imaging in at-risk patients (20–23). The absence of NSF in these patients has been attributed to changing the type of GBCA (from a grade I to a higher-stability grade II or III agent). The outcomes of these two very different strategies—avoidance versus continued use

Advance in Knowledge

- Among 3819 patients with severe (stage 4 or 5) chronic kidney disease (CKD) who underwent gadobenate dimeglumine–enhanced MR imaging, none developed nephrogenic systemic fibrosis (NSF), resulting in a proportion of zero; the exact upper bound of 95% confidence interval was 0.0965%.

Implications for Patient Care

- The risk of NSF to patients with severe CKD after the administration of gadobenate dimeglumine is immeasurably low.
- Commonly used methods of screening patients for contrast-enhanced MR imaging (eg, estimated glomerular filtration rate) may be of low value when gadobenate dimeglumine is administered.

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Abbreviations:
CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
FDA = Food and Drug Administration
GBCA = gadolinium-based contrast agent
NSF = nephrogenic systemic fibrosis

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Guarantors of integrity of entire study, D.R.M., B.K., P.K.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, D.R.M., B.K., K.S., P.K.M.; clinical studies, D.R.M., B.K., A.M., K.S., P.K.M.; statistical analysis, D.R.M., B.K., K.S., S.V.; and manuscript editing, D.R.M., B.K., K.S., S.V., P.K.M.

Conflicts of interest are listed at the end of this article.

See also the editorial by Prince and Weinreb in this issue.

of contrast-enhanced MR imaging, but with a higher-stability GBCA—remains unexplored but has potential significance: Avoidance of contrast-enhanced MR imaging may have unintended adverse outcomes through altered diagnostic results (24).

Uncertainty regarding quantifiable risk of group II or III GBCA exposure in patients who undergo dialysis or those with severe CKD who are at high risk for NSF continues to influence practice patterns. Better measures of this risk may have an effect on future decision-support guidelines and practices. We have created a large single-center database for the evaluation of NSF risk in patients undergoing dialysis or those with severe CKD but who are not on dialysis, who have been exposed to a uniform institutional GBCA protocol for contrast-enhanced MR imaging studies used for assessment of patients before they undergo renal transplant. The purpose of our study was to retrospectively determine the incidence of NSF in patients with severe CKD who underwent a uniform protocol for contrast-enhanced MR imaging with the administration of gadobenate dimeglumine.

Materials and Methods

Patient Selection

This single-center, retrospective study was approved by our institutional review board and compliant with the Health Insurance Portability and Accountability Act. The study included electronic patient records filed between April 2008 and February 2014. We selected only patients with severe CKD who were at high risk for NSF and who were undergoing either peritoneal dialysis or hemodialysis or those with stage 4 or 5 CKD but who were not undergoing dialysis by searching our electronic medical records (version 2102.38; Cerner, North Kansas City, Mo) and the institutional solid organ transplant patient care management software (version 5.4.2.1734.0; OTTR Chronic Care Solutions, Omaha, Neb) for all patients with severe CKD referred for transplant evaluation. A concurrent search of the electronic radiology information system was performed for all patients who had undergone contrast-enhanced MR imaging during the study time window, and the results were cross-referenced with the list of patients referred for kidney transplant evaluation. This method produced a cohort of patients with severe CKD who had undergone at least one institutional protocol–related contrast-enhanced MR examination. This cohort represented a continuation of our earlier report (12), in which patients from an earlier time window were selected (in the previous report, the last date of contrast material administration was March 2008).

Other search criteria and selection filters were as follows: The electronic medical record of each patient was reviewed, with demographic and clinical data recorded for each patient, including age, sex, and estimated glomerular filtration rate (eGFR) (for patients not undergoing dialysis) within 30 days of MR imaging based on both the Modification of Diet in Renal Disease formula and the Chronic Kidney Disease Epidemiology Collaboration equation (25). We did not specifically search for and categorize risk factors for NSF other than the presence of CKD. We documented the type of dialysis at the time of contrast-enhanced MR imaging (classified as peritoneal dialysis, hemodialysis, or none). The date of the latest post–MR imaging full integumentary examination was recorded, and only patients who underwent full integumentary examination at least 6 months after contrast-enhanced MR imaging were included. The number of patients who did not undergo follow-up and documentation with our transplant service, including an integumentary follow-up examination, is unknown.

GBCA Administration

Per institutional protocol, patients referred for renal transplant evaluation underwent contrast-enhanced MR imaging for pretransplant assessment of any potential underlying neoplasm and vascular disease. A single GBCA agent, gadobenate dimeglumine (Multihance; Bracco Diagnostics, Princeton, NJ), was administered according to weight, with a standard dose of 0.05 mmol/kg for MR imaging and 0.1 mmol/kg for MR angiography, followed by a 20-mL saline flush. The dose of gadobenate dimeglumine used for each patient was recorded in the electronic record. In addition, the number of contrast-enhanced MR examinations performed for each patient was recorded, and individual and cumulative doses were calculated. Our institutional protocol requires that, in patients undergoing hemodialysis scheduled for contrast-enhanced MR imaging, the next dialysis session must be performed within 24 hours; patients did not undergo hemodialysis and contrast-enhanced MR imaging if they were not already undergoing hemodialysis before contrast-enhanced MR imaging.

Follow-up

To identify patients who developed NSF after the administration of GBCA, the latest date and type of clinical follow-up that included a full integumentary examination were identified. Full integumentary examinations are protocol for our renal transplant patient evaluations and were documented for all patients included in this study cohort. Skin lesions that were suspicious on the basis of physical examination assessment underwent deep punch or excision biopsy, and the dermatopathologic results were recorded and categorized. A minimum follow-up of 6 months after GBCA administration was set as the threshold for inclusion in the study to ensure adequate time for symptom development. The number of days between the last contrast-enhanced MR examination and the follow-up clinic note and integumentary examination was calculated and recorded.

In addition, a search was undertaken of pathologic information in the electronic medical records by using the search terms "nephrogenic systemic fibrosis" and "NSF" to find all histopathologic specimens of NSF in the pathologic information database. Any positive findings could then be cross-referenced with our patient cohort to

Study Cohort Characteristics

Group	Mean Age (y)	No. of Patients	Sex		Race*				Average No. of Examinations	Average Minimum Follow-up Interval (d)	No. of Skin Biopsies
			M	F	Black	White	Asian	Latino			
Hemodialysis	51	2243	1321	922	1573	595	33	12	1.1	540	134
Peritoneal dialysis	49	405	221	184	224	157	10	1	1.2	477	35
Combined dialysis	47	22	14	8	11	10	1	0	1	576	2
No dialysis	53	1149	676	473	378	389	18	1	1.1	412	48
Total	…	3819	2232	1587	2186	1151	62	14	1.1	501	219

Note.—The eGFR was obtained in the patients who did not undergo dialysis. In those patients, the average eGFR determined with the Modification of Diet in Renal Disease formula was 13.9 mL/min/1.73 m^2, the average eGFR determined with the Chronic Kidney Disease Epidemiology Collaboration equation was 9.2 mL/min/1.73 m^2, the average creatinine level was 4.6 mg/dL, and the average interval between eGFR and MR imaging was 29 days.

* Race was classified on the basis of available records for 3413 of the 3819 patients.

aid in the identification of patients with a histologic diagnosis of NSF.

Statistical Methods

All analyses were performed by using software (version 9.3; SAS Institute, Cary, NC). A Wilcoxon-Mann-Whitney test was used to evaluate any difference in ages between male and female subjects in our study. The proportion of subjects who developed NSF after administration of GBCA and the exact (Clopper-Pearson) 95% confidence intervals were determined by using binomial proportions.

Results

Patients

From January 2008 to February 2014, 3819 patients with severe CKD underwent contrast-enhanced MR imaging per institutional pretransplant protocol and met inclusion and exclusion criteria. Our final study cohort consisted of 1587 female patients (average age, 50 years; age range, 18–79 years) and 2232 male patients (average age, 51 years; age range, 17–83 years); there was no significant difference in age between male and female patients (P = .185). Of the 3819 patients, 312 were also included at the end of a prior study (22), but now with longer follow-up. The detailed characteristics of our patient cohort are summarized in the Table. None of the 3819 patients developed NSF after the administration of gadobenate dimeglumine (resulting in a proportion of zero), and the exact upper bound of 95% confidence interval was 0.0965%.

GBCA Administration

The average volume of gadobenate dimeglumine administered for each contrast-enhanced MR examination was 23 mL (range, 3–45 mL; dose of 0.05 mmol/kg for MR imaging and 0.1 mmol/kg for MR angiography). A fraction of our patient cohort underwent more than one contrast-enhanced MR examination during pretransplant work-up: 182 of the 3819 patients (5%) underwent two examinations, 16 (0.4%) underwent three examinations, and four (0.1%) underwent four examinations.

Follow-up

The average time between the initial MR examination and the most recent clinical examination was 501 days (range, 186–2121 days), with the follow-up intervals shown according to dialysis status in the Table. Biopsies were performed in a total of 219 patients at follow-up examination after MR imaging; Figure 1 summarizes dermatopathologic results, and Figure 2 summarizes the distribution of biopsies according to anatomic location. No patients were diagnosed with NSF at evaluation of biopsy specimens. Forty-six of the 219 biopsies (21%) revealed carcinomas, and the most common malignancy was squamous cell carcinoma (41 of 219 cases, 19%). The most common benign lesions were keratoid lesions (24 of 219 cases, 11%) and melanocytic nevi (23 of 219 cases, 10%).

A search of the pathology database from January 2008 to February 2014 returned no pathologic specimens (biopsy or surgical excision) with a diagnosis of NSF.

Discussion

In our study, we found no patients with newly diagnosed NSF in a large population of patients who underwent contrast-enhanced MR imaging with administration of a single GBCA (gadobenate dimeglumine). To our knowledge, our study represents the largest single-center study of patients with advanced kidney disease exposed to a uniform GBCA-enhanced MR imaging protocol and helps provide a foundation for individualized decisions weighing risk against benefit with regard to the use of contrast-enhanced MR imaging in a patient with advanced CKD. Our study focused on patients at highest risk for NSF, including those with end-stage renal disease who are undergoing hemodialysis or peritoneal dialysis or those with very low eGFR (<30 mL/min/1.73 m^2) who were not yet undergoing dialysis. Moreover, in our study we required a clinical follow-up period of at least 6 months to ensure proper classification of patients with or patients without NSF.

Figure 1

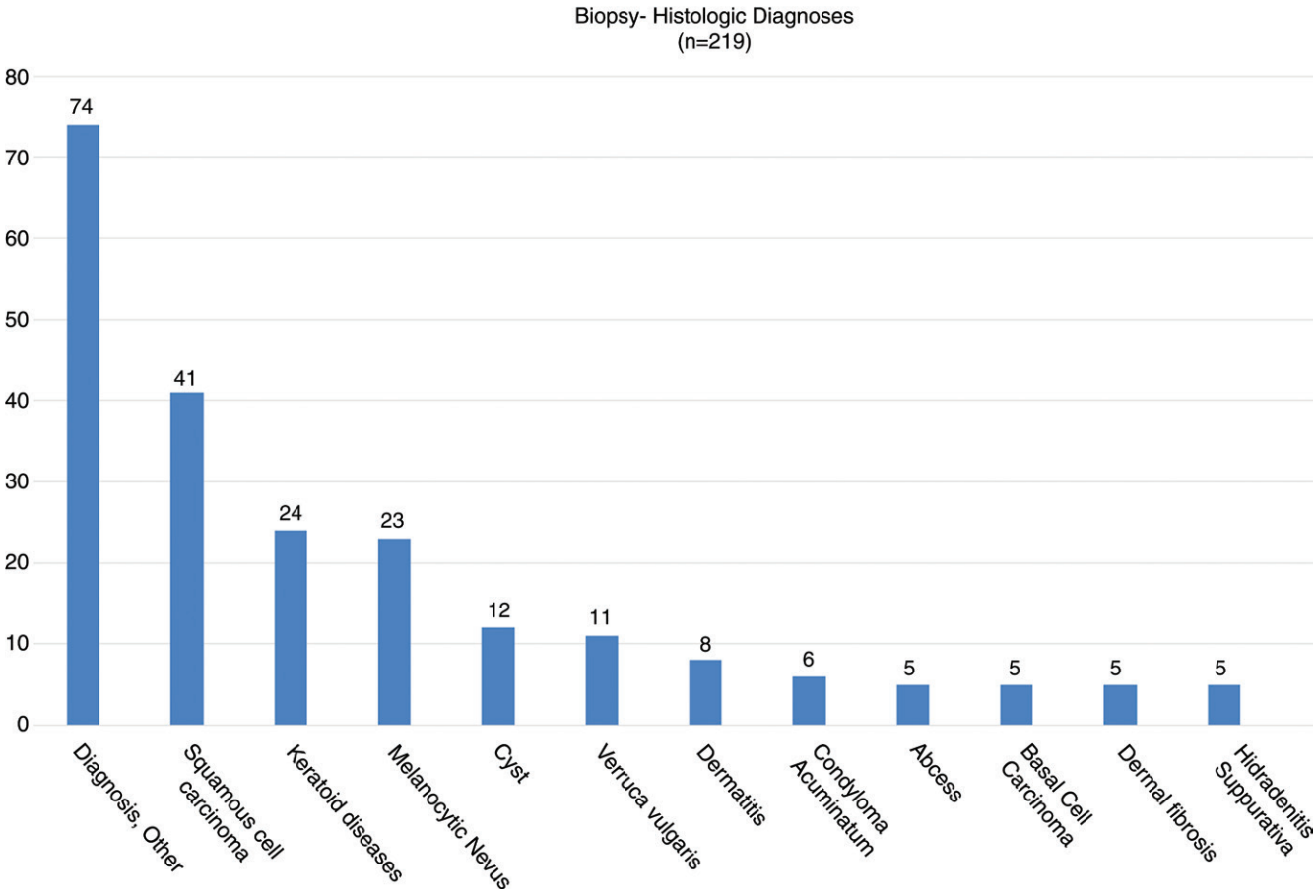

Figure 1: Bar graph shows results of histologic examination of specimens from punch biopsy performed in patients with end-stage renal disease who had previously undergone contrast-enhanced MR imaging. Numbers are numbers of cases.

Our study results contribute to the body of evidence showing that the risk of NSF is related to the type of GBCA used and aligns with multiple previous reports suggesting that certain GBCAs may not be associated with the development of NSF even when administered to patients at the highest risk for development of NSF (stage 4 and stage 5 CKD) (10,21,26). Bruce et al (21) studied 1423 patients with an eGFR of 30 mL/min/1.72 m^2 or lower who had undergone contrast-enhanced MR imaging with gadobenate dimeglumine and also found that no patients developed NSF. Smorodinsky et al (27) evaluated 1167 patients with chronic liver disease who had been exposed to a variety of GBCAs, 843 of whom had some degree of renal insufficiency; none of these

Figure 2

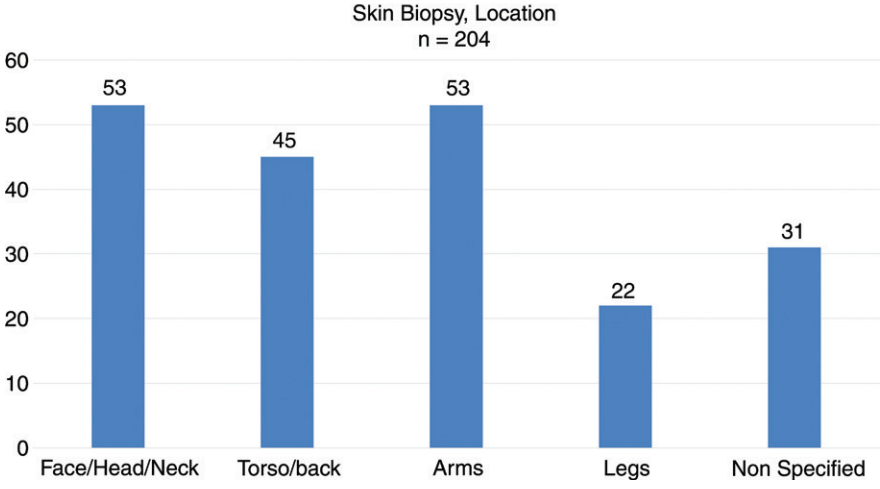

Figure 2: Bar graph shows location of biopsy relative to extremities, torso, or head and neck regions. Numbers are numbers of cases.

patients developed NSF. Our current findings represent an extension of previously reported relative risk from the same institution, as well as that reported by other centers (10,18,20,22,23). Together, these studies have collectively shown no new cases of NSF in thousands of patients with severe CKD who have undergone contrast-enhanced MR imaging with the administration of more stable group II gadolinium chelates (16).

The American College of Radiology guidelines are based on the prediction that linear agents, as a subclass, are more likely to cause NSF. Whereas the three agents accounting for almost all reported patients with NSF are linear GBCAs, the linear agent used in this study (gadobenate dimeglumine) has no unconfounded reports associated with NSF. Reasons for this have yet to be fully determined. Gadobenate dimeglumine is reported to have a 3% clearance through the liver in patients with normal liver and kidney function, likely upregulated in patients with decreased kidney function (15,28). Although the liver clearance rate is relatively minor compared with the kidney pathway, it may represent a beneficial mechanism in patients with kidney disease who are at risk for NSF. Gadobenate dimeglumine is a higher-relaxivity GBCA, and some reports have shown effective diagnostic use at a lower dose (0.05 vs 0.1 mmol/kg) (29), which represents an additional potential factor in NSF risk management, through minimization of dose exposure. Similarly, gadoxetate disodium is another American College of Radiology group II linear GBCA that has a liver clearance of 50% in patients with normal liver and kidney function, a characteristic differentiating this agent from the group I linear agents associated with NSF, which do not have liver clearance; there are no published reports of NSF associated with gadoxetate disodium (30).

It is interesting to note that our study does not provide additional insights into the role of dialysis in protecting patients from NSF. Institutional protocol requires that hemodialysis be performed within 24 hours of GBCA administration if the patient is already undergoing dialysis. However, it is estimated that at least three to five hemodialysis sessions are required to achieve a high level of contrast material elimination. Furthermore, peritoneal dialysis has been noted to effect limited contrast material clearance (31). In our cohort of patients with severe CKD, 10.6% (405 of 3819 patients) underwent only peritoneal dialysis and 30% (1149 of 3819 patients) did not undergo dialysis (either peritoneal dialysis or hemodialysis). Those patients who did not undergo dialysis before MR imaging did not undergo hemodialysis after GBCA administration. As discussed previously, it may be that liver clearance plays a protective role for the agent used in our study or that other factors (yet to be determined) are responsible for the apparent differences in relative NSF risk between gadobenate dimeglumine and other linear agents with higher measured risk.

Limitations of this study include a lack of information regarding GBCA tissue deposition, which we did not measure. The patients with kidney disease included in our study usually had multisystem disorders and required a contrast-enhanced study to obtain information that would affect clinical decisions (32). However, we did not directly assess the rationale for choosing contrast-enhanced MR imaging over other methods, nor did we measure the relative clinical outcomes value of contrast-enhanced MR imaging as compared with alternatives; these determinations were outside the scope of this study.

In summary, our large single-center study demonstrates the safety of performing contrast-enhanced MR imaging with gadobenate dimeglumine in patients with severe CKD, with no patients developing NSF at follow-up integumentary examinations. Our data show that the risk of NSF related to contrast-enhanced MR imaging is sufficiently low to consider use of this diagnostic test when appropriately indicated, even in patients who are undergoing hemodialysis or peritoneal dialysis or those with advanced CKD but who are not yet undergoing dialysis.

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