



A Systematic Review of 639 Patients with Biopsy-confirmed Nephrogenic Systemic Fibrosis

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

See also the editorial by Davenport in this issue.

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Background: Although nephrogenic systemic fibrosis (NSF) affects the use of gadolinium-based contrast agents (GBCAs) in MRI, there continues to be limited knowledge because of the small number of patients with NSF.

Purpose: To perform a systematic review of NSF.

Materials and Methods: PubMed database was searched by using the term “Nephrogenic systemic fibrosis” from January 2000 to February 2019. Articles reporting details on individual patients with NSF diagnosis on the basis of both clinical presentations and biopsy confirmation were included. Data were pooled and authors were contacted for clarifications. Rates of NSF were compared through 2008 versus after 2008 and for group I versus group II GBCAs, assuming equal market share.

Results: Included were 639 patients from 173 articles. Data regarding sex were found for 295 men and 254 women. Age at NSF symptom onset was reported for 177 patients (mean, 49 years \pm 16 [standard deviation]; age range, 6–87 years). There were 529 patients with documented exposure to GBCAs including gadodiamide ($n = 307$), gadopentetate dimeglumine ($n = 49$), gadoversetamide ($n = 6$), gadobutrol ($n = 1$), gadobenate dimeglumine ($n = 1$), multiple ($n = 41$), and unknown ($n = 120$). Among patients with previous exposure, only seven patients were administered GBCA after 2008, yielding a lower rate of NSF after 2008 ($P < .001$). There were motion limitations in 70.8% (296 of 418) of patients, indicating a more serious debilitation. Associated factors reported for NSF included exposure to GBCA group I ($P < .001$), dialysis, proinflammatory conditions, hyperphosphatemia, β -blockers, and epoetin. For 341 patients with follow-up, 12 patients were cured and 72 patients partially improved including one during pregnancy. Among those 84 patients reported as cured or improved, in 34 patients cure or improvement occurred after renal function restoration. Four deaths were attributed to NSF.

Conclusion: Although 639 patients with biopsy-confirmed nephrogenic systemic fibrosis were reported, only seven were after gadolinium-based contrast agent exposure after 2008, indicating that regulatory actions and practice changes have been effective preventive measures. Improvement and sometimes cure with renal function restoration are now possible.

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Nephrogenic systemic fibrosis (NSF) is a systemic disorder characterized by fibrosis and sclerotic-myxedematous skin lesions occurring in individuals with chronic kidney disease stage 4 or 5 (estimated glomerular filtration rate [GFR; eGFR] < 30 mL/min/1.73 m²) or acute renal failure. It was described by Cowper et al in 2000 (1), and in 2006 (2) it was linked with previous exposure to gadolinium-based contrast agents (GBCAs), mostly the nonionic linear GBCA administered at high doses (3). Warnings from the U.S. Food and Drug Administration, European Medical Agency, and other organizations led to widespread screening for renal dysfunction in individuals undergoing GBCA-enhanced MRI and the use of less or no high-risk GBCA when the patient's eGFR was less than 30 mL/min/1.73 m². High-risk group I GBCA per the American College of Radiology contrast media manual includes gadodiamide, gadopentetate dimeglumine, and gadoversetamide.

Since 2008, there have been few reports of NSF related to GBCA exposure, which suggests that the

regulations have been effective. However, there has been relaxation of the requirements for renal function screening with the American College of Radiology manual on contrast media, indicating the assessment of renal function is now optional before administration of low-risk group II GBCAs, including gadoteridol, gadobutrol, gadoterate meglumine, and gadobenate dimeglumine. To learn as much as possible to maintain vigilance against NSF to avoid a resurgence, it is useful to collate data from all prior reported cases. In our study, we performed a systematic review evaluating risk factors and features of NSF.

Materials and Methods

Institutional review board approval was not needed because all data were reported in the literature. One author reported conflicts of interest (Bayer, Bracco, GE Healthcare, Guerbet/Mallinckrodt, and Lantheus). All other authors had no conflicts of interest; therefore, they assessed the data and information.

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Abbreviations

eGFR = estimated GFR, GBCA = gadolinium-based contrast agent, GFR = glomerular filtration rate, NSF = nephrogenic systemic fibrosis

Summary

A systematic search of PubMed identified 639 patients with biopsy-confirmed nephrogenic systemic fibrosis and patient-specific details available for each individual, showing that only seven involved reported exposure to a gadolinium-based contrast agent after 2008.

Key Points

- Per a systematic search of PubMed, only seven patients with biopsy-confirmed nephrogenic systemic fibrosis (NSF) were reported related to exposures to gadolinium-based contrast agents (GBCAs) that occurred after 2008.
- Infants and toddlers younger than 6 years have no reported diagnoses of NSF and adults older than 80 years have only seven reported diagnoses of NSF despite a growing occurrence of reduced glomerular filtration rate in older patients, which suggests that younger and older patients have a reduced risk of NSF.
- Follow-up of patients with NSF shows symptomatic improvements with renal function restoration and with β -blocker cessation, pregnancy, extracorporeal photopheresis, and thiosulfate disodium; cure was reported in 12 patients.

Literature Search Strategy

Two radiology research fellows (H.A. and Y.C., with 4 and 6 years of experience, respectively) independently searched PubMed from January 2000 to February 2019 by using the search terms “Nephrogenic systemic fibrosis,” “Nephrogenic fibrosing dermatopathy,” and “NSF.” Our inclusion criteria included articles that reported patients with NSF diagnosed on the basis of clinical features with biopsy confirmation and articles that reported individual patient details. Retrieved articles were screened and additional manual citation searching was performed on relevant references within each article that met the inclusion criteria after duplicates were removed. Comments, letters, reviews, and articles that did not report individual patients with NSF were excluded on the basis of reviewing titles and abstracts. In total, 639 patients from 173 articles were included (Fig 1), which is nearly double the number of patients in a previous review (4) from 2011 that reported 370 patients from 98 articles.

Bias Assessment

We assessed risk of bias by using A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions, or ACROBAT-NRSI. Patient selection bias was considered severe for case reports, moderate for case series, and low when authors described performing systematic searches of dermatology, pathology, and radiology databases to ensure identification of all patients. Missing data bias was low when reports included age, sex, GBCA type and dose, GFR and/or dialysis status at the time of GBCA exposure, and interval to onset of NSF symptoms; it was considered moderate when up to two parameters were missing; and data bias was severe when more than two parameters were missing. A spreadsheet detailing our extracted data was sent to corresponding authors with a request to verify it and to provide any additional available details.

Outcomes bias was low for articles with final outcomes reported (eg, death, immobility, cure), moderate with some follow-up, and serious with no follow-up. Conflict of interest was graded as low when disclosed as none and moderate when conflict of interest was not disclosed in the study. Serious conflict of interest occurred when an author served as an expert witness in GBCA-related litigation (5) or received support from GBCA manufacturers for the research (6).

Data Extraction

Two authors (H.A. and Y.C.) independently read each article that met inclusion criteria and extracted the data. Laboratory data had to be reported as obtained around the time of GBCA exposure. Additional data extracted included patient age (at time of GBCA exposure, at time of NSF symptom onset, and at time of NSF diagnosis), patient sex, patient ethnicity, motion limitation, internal organ involvement, skin plaques, skin thickening and/or hardening, calcifications, scleral plaque, edema, retroperitoneal fibrosis, thrombosis, imaging studies, MRI indication, history of exposure to gadolinium, and gadolinium type and dose (assuming patients undergoing MR angiography received a double-dose GBCA of 30 mL). Other data included chronic or acute renal failure at the time of GBCA exposure, underlying reason for renal dysfunction, dialysis at the time of GBCA exposure, type of dialysis, interval between GBCA exposure and next dialysis, interval between GBCA exposure and onset of symptoms attributed to NSF, blood urea nitrogen and/or creatinine, eGFR, calcium, phosphorus, acidosis, sedimentation rate, epoetin treatment, kidney transplant, any improvement after transplantation or renal function restoration, and liver disease and/or transplant; proinflammatory conditions including autoimmune disease, diabetes, recent surgical procedure, infection, shock, malignancy, myocardial infarction, gout, and vasculitis; and treatments and outcomes including improvement, progression, or death. All discrepancies and differences in the data extractions between the two observers were resolved by consensus.

Statistical Analysis

Data were reported as mean \pm standard deviation when normally distributed or as median, mode, and interquartile range when not normally distributed. Incidence of NSF associated with group I versus group II GBCA was calculated by assuming equal market share. Sensitivity of the significance of the difference to this market share assumption was assessed by varying market share over a broad range. Incidence of NSF through 2008 versus after 2008 was calculated by assuming equal GBCA utilization for those two periods (ie, before vs after the black box warning and implementation of GBCA regulatory restrictions that occurred in 2008) and compared with χ^2 . The effect of cumulative GBCA dose, dialysis status at GBCA exposure, type of dialysis, acute versus chronic renal failure, and GBCA exposure to NSF symptom onset interval on the incidence of motion limitations reported with NSF was assessed by multivariate regression analysis including parameters found to be significant at univariate analysis. Statistical analysis was performed by using statistical software (R version 3.5.3; R Core Team, Vienna, Austria) and the α level was set to .05.

Results

Study and Patient Selection

The database search identified 1073 articles. By screening titles or abstracts, 841 articles were removed. The other 232 articles were assessed at the full-text level. Of these, 59 articles were excluded because of the following: no biopsy confirmation ($n = 2$), duplicate reporting ($n = 21$), no patient with NSF in study ($n = 20$), summary data ($n = 15$, which summarized 82 patients), and lack of author response to a letter challenging the diagnosis ($n = 1$) (7,8). From the remaining 173 articles (3,5,6,9–178) reporting 794 patients, 155 patients were excluded for the following reasons (Fig 1): no biopsy confirmation ($n = 59$), overlap with other articles ($n = 49$), no details ($n = 46$), and change of diagnosis ($n = 1$) (9), yielding 639 patients from which data could be pooled.

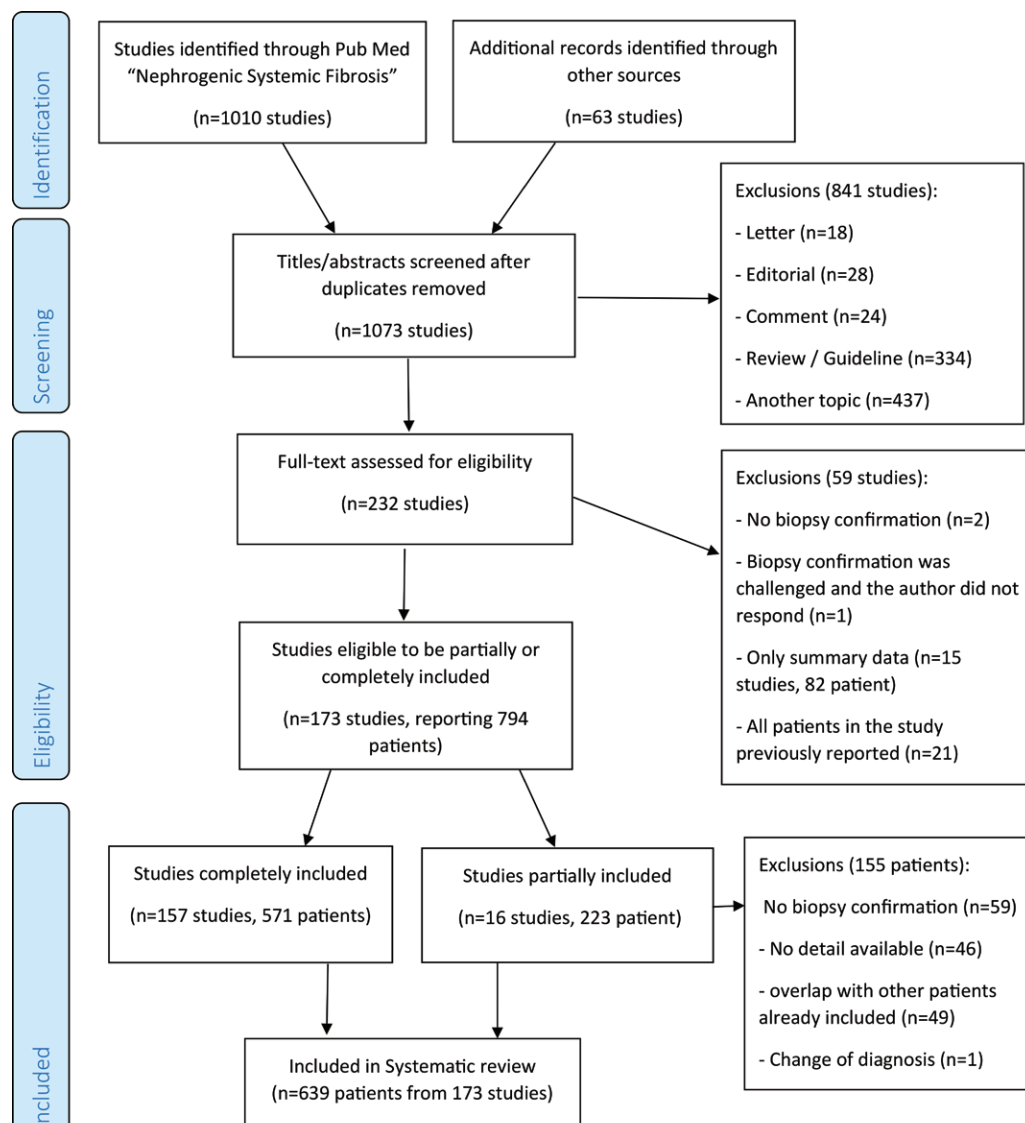


Figure 1: Flowchart of study and patient selection process.

Bias Assessment

We found a moderate risk of bias because of missing data in 85 articles and severe risk in 28 articles. Authors were contacted to resolve these biases and 72 authors provided additional information. Two articles had serious conflicts of interest (7,8) and 65 disclosed no conflict. For all of the articles, severe confounding bias was present because all patients had renal dysfunction and other comorbidities, which may have contributed to many reported symptoms and findings. Selection bias was severe for 126 case reports and moderate for six case series. Outcome bias was low for 101 articles that reported final outcomes and severe for 37 articles with no follow-up (Table 1).

Data Extraction Results

Patient demographics.—Among 549 patients for whom data on sex were available, 295 were men and 254 were women.

Ethnicity was reported for 351 patients, and it included the following: white, 228 patients; black or African American, 68 patients; Hispanic, 15 patients; Japanese, 20 patients; Chinese, four patients; Malay, one patient; Vietnamese, two patients; Taiwanese, three patients; unspecified Asian, three patients; Indian, four patients; Middle Eastern, one patient; and Maori, two patients. Data regarding patient age were available for 130 patients at GBCA exposure (mean age, 49 years \pm 16), 177 patients at NSF symptom onset (mean age, 49 years \pm 16) (Fig 2), and 414 patients at diagnosis (mean age, 51 years \pm 16). There were no reports of NSF in neonates or toddlers; the youngest age reported was 6 years. There were only seven reports in older patients (>80 years); the oldest patient reported was 87 years.

Extent of disease.—Dermatologic manifestations without motion limitations were reported for 29.2% (122 of 418) of

Table 1: Bias Risk for Data in Patients with Nephrogenic Systemic Fibrosis

Type of Bias	Low	Moderate	Severe
Confounding	0/0	0/0	173/639
Selection of patients	41/458	6/26	126/155
Missing data	60/241	85/349	28/49
Measurement of outcomes	101/295	35/161	37/183
Conflict of interest	65/250	106/364	2/25

Note.—Data are number of articles/number of patients. Data includes 173 studies that reported a total of 639 patients.

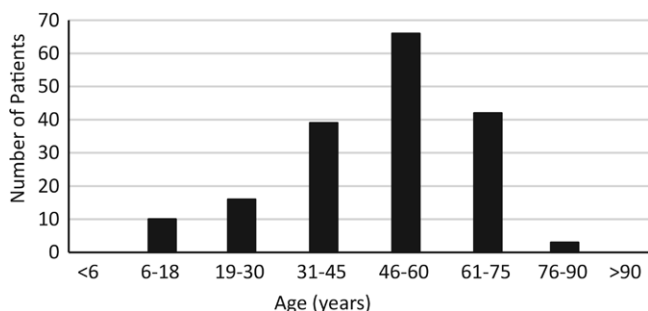


Figure 2: Age at onset of nephrogenic systemic fibrosis symptoms for 177 patients with nephrogenic systemic fibrosis.

patients with data, which indicated a milder form of the disease. Three patients had peau d’orange involving the breast that reportedly resembled inflammatory breast cancer (10–12). Although NSF generally spares the face, three reports described bilateral firm papules or lesions on the lateral canthal area (13,14). Motion limitations developed in 70.8% (296 of 418) of patients, and this represented a more debilitating disease. Internal organ involvement was reported in 56% (51 of 91; Table 2) and autoimmune disease in 47.5% (68 of 143; Table 3). Characteristics of the disease and reported contributing factors are summarized in Table 4.

GBCA.—For 539 patients with data, 97.4% (525 of 539) were exposed to GBCA before they developed NSF but only seven underwent administration of GBCA after 2008 (15–17,126,141,164,179). NSF occurred in 14 patients without evidence of prior GBCA exposure in spite of searching. Ninety-eight articles ($n = 405$) reported type of GBCA (Table 5), showing that 362 patients were administered only group I GBCAs. Group II GBCA exposure was reported in 23 patients, but only two were unconfounded (17,18) and two additional patients were administered gadoterate with another unknown GBCA, precluding an assessment of confounding (19). Accuracy and completeness of these data were sometimes questioned (3,8).

The interval between GBCA exposure and NSF was available for 336 patients, ranging from the same day to approximately 10 years (median, 42 days; mode, 30 days; interquartile range, 19–90 days). For patients in whom GBCA dose was reported or could be estimated from the examination type, 6.7% (19 of 282) of patients were administered a standard dose (0.1 mmol/kg) or lower, and 93.3% (263 of 282)

Table 2: Internal Organ Involvement in Patients with Nephrogenic Systemic Fibrosis

Involved Internal Organ	No. of Patients*
Heart (muscle, valves, pericardium)	19
Lung (parenchyma, pleura)	12
GI (pancreas, adrenal glands, esophagus, liver, intestines)	9
CNS (dura mater, meninges)	8
Kidneys	7
Muscle	5
Diaphragm	3
Vessels	3
Thyroid	1
Not specified	11
Total no. with involvement	51
No internal organ involvement	40

Note.—There were a total of 91 patients with nephrogenic systemic fibrosis. CNS = central nervous system, GI = gastrointestinal.

* Twelve patients had more than one internal organ involved with nephrogenic systemic fibrosis.

of patients were administered a greater than standard dose. Multiple exposures occurred in 173 patients. The mean cumulative dose was estimated to be 63 mL.

Dialysis and renal failure.—Of 322 patients with data, 278 (86.3%) were on dialysis around the time of GBCA exposure. For 89 patients, interval between GBCA exposure and dialysis could be determined; 27 patients underwent dialysis the same day, 23 patients underwent dialysis 1 day later, 10 patients underwent dialysis 2 days later, and 29 patients underwent dialysis 3 or more days later. Among patients not on dialysis with eGFR data (mean, 14.3 mL/min/1.73 m² ± 8), three had eGFR greater than 30 mL/min/1.73 m² but all three had acute renal failure resulting in eGFR overestimation (20–22). Another two patients were reported to have creatinine clearances of 37 and 51 mL/min (23). However, both had a body mass index greater than 25 kg/m², indicating that their GFR was actually lower (180). The underlying causes of renal failure are shown in Table 6.

Type of MRI.—MRI examination type (Table 7) was reported for 239 patients, including 46.4% (111 of 239) undergoing MR angiography, which likely reflected the common use of high doses for this examination until 2008. Abdominal MRI was the second most common examination (22.2%; 53 of 239), which also likely reflects the tendency to have administered high doses for liver MRI before 2008. Interestingly, there were only four patients who underwent 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 these patients. Imaging features reported include soft-tissue activity at bone scintigraphy ($n = 6$), skin thickening at mammography ($n = 5$), and inflammatory changes on CT scans ($n = 15$).

Table 3: Autoimmune Disease Assessed in Patients with Nephrogenic Systemic Fibrosis

Type of Autoimmune Disease	No. of Patients
Systemic lupus erythematosus	39
Antiphospholipid syndrome	12
IgA nephropathy	4
Rheumatoid arthritis	2
Wegner granulomatosis	1
Multiple sclerosis	1
Henoch-Schonlein purpura	1
Good pasture syndrome	2
Goiter	1
Unspecified	5
Total	68

Note.—IgA = immunoglobulin A.

Outcomes.—For those with follow-up, 24.6% (84 of 341) had partial ($n = 72$) or complete ($n = 12$) resolution of NSF symptoms, and 40% (34 of 84) of resolutions of symptoms occurred after restoration of renal function. Improvement was also reported during pregnancy (22); however, a confounding variable in that patient was implementation of dialysis five times per week. Five patients who were administered high-dose β -blockers had symptomatic improvement at cessation of β -blockers (23). Another patient in the same study improved by switching from subcutaneous administration of darbepoetin to intravenous administration of darbepoetin.

The clinical course was stable in 61 patients and progressive in 20 patients. Four patients were dependent on a walker, 20 patients were wheelchair bound, and 10 patients were described as severely disabled. Death was noted in 110 patients, but only four attributed death to NSF after administration of 20, 32, 50, and 75 mL of linear GBCA (Table 8).

Data Analysis

By assuming equal market share for groups I and II GBCAs, the rate of NSF per million exposures to group I was 1.52 (95% confidence interval: 1.37, 1.68) versus 0.008 (95% confidence interval: 0.001, 0.032) for group II ($P < .001$). A market share sensitivity analysis showed the rate of NSF per million exposures was still significantly (ie, 20-fold) higher for group I GBCA by assuming 90% market share of 0.84 (95% confidence interval: 0.76, 0.93) versus group II with 10% market share of 0.04 (95% confidence interval: 0.006, 0.16; $P < .001$).

By assuming equal use of GBCA before versus after the implementation of black box warnings and implementation of GBCA regulatory restrictions, the rate of NSF per million exposures was 2.07 (95% confidence interval: 1.90, 2.26) through 2008 versus 0.028 (95% confidence interval: 0.012, 0.060) after 2008 ($P < .001$). No statistically significant effects were observed regarding developing motion limitations during the course of the disease with cumulative GBCA dose, dialysis, type of dialysis, acute or chronic renal failure, and GBCA exposure to NSF interval.

Table 4: Patient Demographics and Nephrogenic Systemic Fibrosis Characteristics

Parameter	No. of Patients
Demographic	
Mean age at onset of NSF symptoms (y)*	49 \pm 16 (6–87) [177]
No. of men	295/549 (53.7)
No. of women	254/549 (46.3)
Features of NSF	
Skin plaques	403/418 (96.4)
Skin thickening/hardening	398/418 (95.2)
Edema	297/418 (71.0)
Scleral plaque/injection	41/418 (9.8)
Only dermatologic manifestation without motion limitation	122/418 (29.2)
Dermal calcification	29
Motion limitation	296/418 (70.8)
Joint contractures	211/296 (71.3)
Stiffness	19/296 (6.4)
Unspecified	66/296 (22.3)
Internal organ involvement	51/91 (56)
Contributing factors	
Dialysis at time of GBCA	309/377 (82.0)
Hemodialysis	243/309 (78.6)
Peritoneal dialysis	35/309 (11.3)
CVVH	4/309 (1.3)
Unspecified dialysis	27/309 (8.7)
Renal failure	
Acute	109/556 (19.6)
Chronic	449/556 (80.8)
Kidney transplant	143/631 (22.7)
Failing renal transplant	86/143 (60.1)
Liver disease	43
Transplant	23
Proinflammatory events	363/380 (95.5)
Recent major surgery	103
Diabetes	115
Acute thrombosis	80
Infection	71
Autoimmune disease	68/143 (47.6)
Malignancy	36
Other (ie, gout, myocardial infarction, vasculitis, shock)	34
Acidosis	38/55 (69)
Hyperphosphatemia [†]	75/103 (72.8)
Epoetin	79/128 (61.7)
β -blockers	22/55 (40)

Note.—Unless otherwise indicated, data are total number of patients/number of patients with nephrogenic systemic fibrosis for whom it was determined that the given feature was assessed; data in parentheses are percentages. CVVH = continuous venovenous hemofiltration, GBCA = gadolinium-based contrast agent, NSF = nephrogenic systemic fibrosis.

* Data in parentheses are range; data in brackets are the number of patients with these data.

[†] Mean serum phosphorus level, 5.6 mg/dL \pm 2 (healthy range, 2.5–4.5 mg/dL).

Table 5: Type of GBCA Used in Patients with Nephrogenic Systemic Fibrosis

Type of GBCA	GBCA Structure	No. of Patients
Gadodiamide	Nonionic Linear	307/405 (75.8)
Gadoversetamide	Nonionic Linear	6/405 (1.5)
Gadopentetate dimeglumine	Ionic Linear	49/405 (12.1)
Gadobutrol	Macrocylic	1/405 (0.2)
Gadoterate meglumine	Macrocylic	0–2*/405 (0–0.5)
Gadoteridol	Macrocylic	0/405 (0)
Gadoxetic disodium	Ionic Linear	0/405 (0)
Gadobenate dimeglumine	Ionic Linear	1/405 (0.2)
Multiple agents including gadodiamide		33/405 (8.1)
Multiple not including gadodiamide		8/405 (2.0)
Unknown		120

Note.—Data are numerator/denominator; data in parentheses are percentages. Data are from 405 patients with nephrogenic systemic fibrosis. GBCA = gadolinium-based contrast agent.

* Two patients were exposed to gadoterate and another unknown GBCA.

Discussion

We identified 639 patients with biopsy-confirmed nephrogenic systemic fibrosis (NSF) and sufficient details for each individual that showed almost all were administered gadolinium-based contrast agents (GBCAs), primarily nonionic linear, at high doses (>0.1 mmol/kg). This supports the hypothesis that GBCA can trigger NSF, but there may be other triggers because 14 patients with NSF were not administered GBCA. Proinflammatory events, epoetin, hyperphosphatemia, acidosis, and β -blockers were all reported as contributing factors. Among patients on dialysis, some may have had poor quality dialysis because of failing dialysis fistula, use of peritoneal or continuous venovenous hemofiltration approaches, or delay longer than 3 days between GBCA and dialysis. This further supports the recommendations to administer the GBCA just before a regular dialysis session in patients on hemodialysis (181).

After dialysis, the most common clinical situation was a kidney transplant that failed in a patient who underwent GBCA-enhanced MR angiography. Fortunately, it is possible to evaluate transplant arteries without GBCA by using ferumoxytol-enhanced or noncontrast-enhanced renal MR angiography (182). MR angiography with standard or lower than standard dose group II GBCAs, contrast-enhanced CT, and Doppler US are additional options (183,184).

A large number of patients were administered nonionic linear GBCAs (gadodiamide, gadoversetamide), which tend to have lower in vitro stability compared with the ionic linear and macrocylic agents; this supports the hypothesis that lower chelate stability contributes to greater risk of NSF (24,25,185). However, this does not necessarily translate into greater overall risk, especially in patients with normal renal function, because

Table 6: Cause of Underlying Renal Disease in Patients with NSF

Underlying Renal Disease	No. of Patients
Diabetic nephropathy	48
Glomerulonephritis	37
Hypertensive nephropathy	35
Chronic kidney disease	29
Autoimmune nephropathy	19
Acute kidney injury	17
FSGS*	16
Genetic renal abnormalities	14
Hepatorenal syndrome	10
Renovascular disease	9
ESRD* from unknown reason	8
Pyelonephritis	8
Reflux nephropathy	7
Drug-induced nephropathy	6
Malignancy	5
IgA nephropathy	3
Nephrolithiasis	3
Eclampsy	2
Interstitial nephritis	3
Ischemia	2
HELLP syndrome	1
Obstructive nephropathy	1
Osteodystrophy	1
Postpartum HUS*	1
Sarcoidosis	1
Other	16

Note.—Data are from 287 patients with nephrogenic systemic fibrosis. ESRD = end stage renal disease; FSGS = focal segmental glomerulonephritis; HELLP = hemolysis, elevated liver enzymes, low platelet count; HUS = hemolytic uremic syndrome; IgA = immunoglobulin A; NSF = nephrogenic systemic fibrosis.

* Some patients had more than one underlying kidney disease.

nonionic agents have fewer serious allergic-type adverse events and deaths (26,186).

The near elimination of new patients since 2008 indicates that regulatory recommendations to avoid GBCAs in patients with GFR less than 30 mL/min/1.73 m² are preventing NSF and preserving access to the benefits of GBCAs for most patients. Because macrocylic GBCAs have been used in Europe without renal function screening, it would appear these do not cause NSF. Indeed, because the risk is sufficiently low or possibly nonexistent, American College of Radiology contrast media manual suggests that renal function assessment before group II GBCA administration is not necessary. As in all instances, it should be administered at the lowest dose possible and only if they are deemed necessary. The single patient who develops NSF related to macrocylic GBCA (18) may be a rare exception, may have had another GBCA exposure, or may have developed NSF from a cause unrelated to GBCA.

NSF risk appears to be related to age. No patients younger than 6 years developed NSF, despite babies with immature kidneys and low GFR who were administered GBCAs, sometimes at high doses (eg, for congenital heart disease workups). We do

Table 7: Gadolinium-based Contrast Agent-enhanced Imaging Studies Preceding Nephrogenic Systemic Fibrosis

GBCA Examination Type	No. of Patients
MR angiography	111
Abdomen	53
Head	31
Radiographic angiography	29
Extremities	14
Unspecified	13
Pelvis	29
Spine	15
Cardiac	4

Note.—GBCA = gadolinium-based contrast agent.

Table 8: Outcomes

Outcome	No. of Patients
Cure (ie, complete resolution of symptoms)	12/341 (3.5)
Improvement (ie, partial resolution of symptoms)	72/341 (21.1)
Improvement or cure after renal function restoration	34/341 (10.0)
Dependent on walker	4/341 (1.2)
Wheelchair bound	21/341 (6.2)
Worsening and severely disabled	30/341 (8.8)
Stable	61/341 (17.9)
Alive (without further details)	31/341 (9.1)
Death*	110/341 (32.3)

Note.—Data are numerator/denominator; data in parentheses are percentages. Data are from 341 patients with nephrogenic systemic fibrosis who had follow-up information.

* Four of these deaths were attributed to nephrogenic systemic fibrosis.

not know why the young immune system is not susceptible to gadolinium triggering of NSF. The paucity of older patients (age > 80 years), in spite of a high prevalence of renal insufficiency in this population, suggests that their immune systems may not respond as vigorously to the NSF trigger as that of younger adults. Alternatively, these patients may somehow have been less likely to have been administered group I GBCAs or their NSF symptoms are less evident.

Unlike 10 years ago, when to our knowledge there were no treatment options, there are now reports of symptomatic improvement and even cure following normal renal function restoration (eg, via transplantation or resolution of acute renal failure), pregnancy, cessation of β -blockers, administration of sodium thiosulfate, and extracorporeal photopheresis.

Our study had limitations. The limitations include severe confounding bias in all articles and substantial number with selection bias, missing data bias, limited outcomes, and conflicts of interest. However, these biases are balanced against the large total number, which may average out the effects of opposing biases. Incomplete information from 72 studies was mitigated by contacting authors. However, authors who depend on their clinical

expertise tended to focus on reporting different aspects of NSF. In particular, most case reports were exploratory and did not systematically indicate the absence of positive findings. Also, we did not correct numbers of NSF reports for each GBCA according to market share or for the tendency toward over-reporting by academic centers. Thus, high market share of gadopentetate and gadodiamide at academic centers before 2008 may have resulted in larger numbers of NSF reports compared with the other group I GBCA, gadoversetamide. One hospital reported the same rate of NSF after switching to gadoversetamide that they noticed previously with gadodiamide. Finally, these data are limited by the absence of a control population, although some individual reports did include control patients.

This information from 639 biopsy-confirmed patients with nephrogenic systemic fibrosis can help to continue preventing new patients. Group I gadolinium-based contrast agents (GBCAs) need to be avoided in patients with a glomerular filtration rate less than 30 mL/min/1.73 m²; however, there is no need for screening of renal function if the patient is exposed to GBCA group II. For patients on regular hemodialysis, GBCA-enhanced MRI should be scheduled for just before the next dialysis session.

Author contributions: Guarantor of integrity of entire study, H.A.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, H.A., Y.C., M.R.P.; clinical studies, T.R.E.; statistical analysis, H.A., Y.C., Y.Z.; and manuscript editing, H.A., T.R.E., Y.Z., M.R.P.

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