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Risk of Nephrogenic Systemic Fibrosis in Patients With Stage 4 or 5 Chronic Kidney Disease Receiving a Group II Gadolinium-Based Contrast Agent
A Systematic Review and Meta-analysis

Sean A. Woolen, MD, MS; Prasad R. Shankar, MD; Joel J. Gagnier, ND, MSc, PhD; Mark P. MacEachern, MLIS; Lisa Singer, MD, PhD; Matthew S. Davenport, MD

IMPORTANCE Risk of nephrogenic systemic fibrosis (NSF) to individual patients with stage 4 or 5 chronic kidney disease (CKD; defined as estimated glomerular filtration rate of <30 mL/min/1.73 m^2) who receive a group II gadolinium-based contrast agent (GBCA) is not well understood or summarized in the literature.

OBJECTIVE To assess the pooled risk of NSF in patients with stage 4 or 5 CKD receiving a group II GBCA.

DATA SOURCES A health sciences informationist searched the Ovid (MEDLINE and MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citation, and Daily and Versions), Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Open Grey databases from inception to January 29, 2019, yielding 2700 citations.

STUDY SELECTION Citations were screened for inclusion in a multistep process. Agreement for final cohort inclusion was determined by 2 blinded screeners using Cohen κ. Inclusion criteria consisted of stage 4 or 5 CKD with or without dialysis, administration of an unconfounded American College of Radiology classification group II GBCA (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, or gadoteridol), and incident NSF as an outcome. Conference abstracts, retracted manuscripts, narrative reviews, editorials, case reports, and manuscripts not reporting total group II GBCA administrations were excluded.

DATA EXTRACTION AND SYNTHESIS Data extraction was performed for all studies by a single investigator, including publication details, study design and time frame, patient characteristics, group II GBCA(s) administered, total exposures for patients with stage 4 or stage 5 CKD, total cases of unconfounded NSF, reason for GBCA administration, follow-up duration, loss to follow-up, basis for NSF screening, and diagnosis.

MAIN OUTCOMES AND MEASURES Pooled incidence of NSF and the associated upper bound of a 2-sided 95% CI (risk estimate) for the pooled data and each of the 4 group II GBCAs.

RESULTS Sixteen unique studies with 4931 patients were included (κ = 0.68) in this systematic review and meta-analysis. The pooled incidence of NSF was 0 of 4931 (0%; upper bound of 95% CI, 0.07%). The upper bound varied owing to different sample sizes for gadobenate dimeglumine (0 of 3167; upper bound of 95% CI, 0.12%), gadoterate meglumine (0 of 1204; upper bound of 95% CI, 0.31%), gadobutrol (0 of 330; upper bound of 95% CI, 1.11%), and gadoteridol (0 of 230; upper bound of 95% CI, 1.59%).

CONCLUSIONS AND RELEVANCE This study's findings suggest that the risk of NSF from group II GBCA administration in stage 4 or 5 CKD is likely less than 0.07%. The potential diagnostic harms of withholding group II GBCA for indicated examinations may outweigh the risk of NSF in this population.

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Author Affiliations: Department of Radiology, University of Michigan, Ann Arbor (Woolen, Shankar, Davenport); Michigan Radiology Quality Collaborative, University of Michigan, Ann Arbor (Woolen, Shankar, Davenport); Department of Orthopaedic Surgery, University of Michigan, Ann Arbor (Gagnier); Department of Epidemiology, University of Michigan, Ann Arbor (Gagnier); Taubman Health Sciences Library, University of Michigan, Ann Arbor (MacEachern); Dana-Farber Cancer Institute, Department of Radiation Oncology, Brigham and Women's Hospital, Boston, Massachusetts (Singer); Department of Urology, Michigan Medicine, Ann Arbor (Davenport).

Corresponding Author: Prasad R. Shankar, MD, Department of Radiology, University of Michigan, 1500 E Medical Center Dr, Room B2 A209P, Ann Arbor, MI 48109 (pshankar@med.umich.edu).

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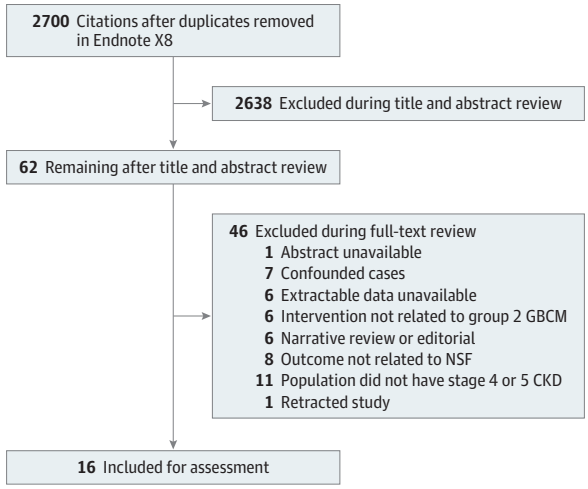
Nephrogenic systemic fibrosis (NSF) is a rare, potentially fatal condition caused by iatrogenic gadolinium administration in patients with acute kidney injury or stage 4 or 5 chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2.[1-4] After more than 500 cases of NSF were reported from 1997 to 2007, regulations were adopted to prevent NSF.[5] In 2007, the US Food and Drug Administration mandated a black box warning advising avoidance of all gadolinium-containing contrast agents (GBCA) in at-risk patients.[5] The label was updated in 2010 to contain recommendations for health care professionals regarding kidney function screening, use of lower-risk GBCAs, and decreasing GBCA dose.[6] Such recommendations informed hospital policies and were successful in effectively eliminating the disease.[7-9] However, they also resulted in denial or delay of clinically indicated, contrast-enhanced magnetic resonance imaging (MRI) in patients with severe kidney disease, resulting in the undermeasured indirect harms of misdiagnosis and delayed diagnosis.[10] In addition, the guidelines were applied to all GBCAs regardless of gadolinium-chelate lability or association with NSF.[11,12]

Accumulating literature[8,13-27] and newer guidelines[28,29] have recognized that not all GBCAs have the same risk of NSF. The American College of Radiology (ACR) manual on contrast media, version 10.3[28] and the European Society of Urogenital Radiology guidelines on contrast agents, version 10.0[29] recognize differences in risk of NSF between GBCAs and classify GBCAs into 3 distinct (albeit slightly different) groups.[28,29] The ACR terms the lowest-risk GBCAs as group II agents (gadobenate dimeglumine, gadoteridol, gadoterate meglumine, and gadobutrol), representing those GBCAs with "very low, if any, risk of NSF development."[28(p85)] Both guidelines have been updated recently to indicate that, for the lowest-risk GBCAs, kidney function measurement is not obligatory and that indicated contrast-enhanced MRI with a low-risk GBCA should not be denied on the basis of NSF risk alone.[28,29]

Figure 1. Study Flow Diagram



Key Points

Question What is the risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent?

Findings In this systematic review and meta-analysis of 16 unique studies and 4931 patients, the pooled incidence of nephrogenic systemic fibrosis after administration of a group II gadolinium-based contrast agent in patients with stage 4 or 5 chronic kidney disease was 0%; the upper bound of the 95% CI was 0.07%.

Meaning Findings suggest that the risk of nephrogenic systemic fibrosis from group II gadolinium-based contrast agent administration in stage 4 or 5 chronic kidney disease is likely less than 0.07%; potential diagnostic harms of withholding group II gadolinium-based contrast agents for indicated examinations may outweigh the risk of nephrogenic systemic fibrosis in this population.

Unfortunately, the specific risk to individual patients is not well understood or summarized in the literature. Knowledge of this risk is important for counseling and risk-benefit decision-making in individual patients. Establishing these risk estimates may provide an evidence basis for policy makers and physicians who otherwise may hesitate to administer these agents to patients with stage 4 or 5 CKD. The purpose of this systematic review and meta-analysis is to assess the pooled risk of NSF in patients with stage 4 or 5 CKD receiving a group II GBCA.

Methods

This systematic review and meta-analysis was compliant with the Health Insurance Portability and Accountability Act and was exempt based on University of Michigan institutional review board exemption self-regulated status owing to the use of published data with no new study participants. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[30]

Eligibility Criteria

Included studies evaluated human participants with stage 4 or 5 CKD (eGFR, <30 mL/min/1.73 m^2) and/or receiving dialysis who underwent administration of a group II GBCA (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, or gadoteridol). The outcome measure required for inclusion was assessment of unconfounded incidence of NSF. All follow-up interval lengths were included. Conference abstracts, retracted manuscripts, narrative reviews, editorials, case reports, and manuscripts not reporting total group II GBCA administrations were excluded (**Figure 1**).

Data Sources and Searches

Comprehensive searches were performed by an expert health sciences informationist (M.P.M.) from inception to January 29, 2019, in the following databases: Ovid (MEDLINE and MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citation, and Daily and Versions), Embase, Cochrane Central Register of Controlled Trials (Wiley), Web of Science (Clarivate), and Open Grey. Each search consisted of CKD and

group II GBCA concept blocks, with combinations of controlled headings (when possible) and title, abstract, and keyword terms. No date, language, or other restriction were incorporated into the searches. Duplicate citations were removed in Endnote X8 (Clarivate Analytics). Complete search strategies are available in eMethods 1 in the Supplement.

Study Selection

Studies were screened for inclusion using a multistep process summarized in the study flow diagram (Figure 1). Search results returned 2700 citations, which were screened at the title and abstract level by 2 study team members (1400 by P.R.S. and 1300 by S.A.W.). A sample set of 100 citations was randomly cross-reviewed by the study team member with more years of experience (P.R.S.) to ensure consistency.

After the initial screening, the remaining citations (n = 62) were all reviewed at the manuscript level by 2 blinded study team members (S.A.W. and P.R.S.) (eMethods 2 in the Supplement). Agreement for inclusion was calculated using the Cohen κ with the following scale[31]: 0.01 to 0.20 indicates slight; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 0.99, almost perfect. Disagreements were resolved by consensus discussion. A third study team member (M.S.D.) adjudicated when needed.

Data Collection and Data Items

Data extraction was performed for all studies by a single study team member (P.R.S.). Extracted data included publication details, study design and time frame, patient characteristics, group II GBCA(s) administered, total exposures for patients with stage 4 or 5 CKD, total cases of unconfounded NSF, reason for GBCA administration, follow-up duration, loss to follow-up, basis for NSF screening, and diagnosis.

Risk of Bias Analysis

Risk of bias analysis of the included studies was performed by a single study team member (P.R.S.). Criteria used for assessment were based on previously described measures for nonrandomized cohort studies.[32] Each possible source of bias was assessed as being fulfilled (yes, meaning bias is unlikely to be present), unfulfilled (no, meaning bias is likely to be present), or unknown (meaning information is inadequate or inapplicable to study design). Certain components of the risk of bias assessment were scored as not applicable when inapplicable to study design or results.

Statistical Analysis

The principal summary measure is the pooled incidence of NSF and associated upper bound of the 95% CI (risk estimate) in patients with stage 4 or 5 CKD receiving a group II GBCA. Subanalyses were performed to assess risk estimates on a per-study basis and for each of the 4 individual group II GBCAs. Data analysis was performed with Stata, version 15.2 (StataCorp LLC).

Results

Initial database searches returned 2700 unique citations (Figure 1). After title and abstract review, 62 potential citations remained. After full text review, a final cohort of 16 citations including 4931 patients was available for analysis. Interrater agreement in determining the final study cohort from the 62 screened citations was substantial (κ = 0.68; 95% CI, 0.49-0.87).

Characteristics of included studies are provided in **Table 1**.[8,13-27] Studies were published from May 2008 through April 2019. The time frame of investigation across all studies spanned 1997 through 2017. The included studies were a mix of retrospective cohort (11 of 16 [69%]) and prospective cohort (5 of 16 [31%]) designs. Study representation was international, with most of the studies performed in Europe, including 2 multiple-country studies (8 of 16 [50%]) and the United States (7 of 16 [44%]). Multicenter studies constituted 7 of 16 (44%) of the included cohort.

The incidence of NSF in patients with stage 4 or 5 CKD across all 16 studies was 0 of 4931 (0%). The upper bound of the 2-sided 95% CI (1-sided 97.5% CI) for this pooled estimate was 0.07% (**Figure 2**). Study-specific details regarding characteristics of GBCA exposure, number of GBCA exposures, and reference standard for NSF assessment are provided in **Table 2**.

Upper bounds of 95% CIs varied on a study-specific basis (0.26%-52.2%) owing to differences in study-specific eligible sample sizes (Figure 2). Follow-up intervals for NSF detection ranged from 3 to 72 months; follow-up interval was unknown in 2 of 16 studies. The reference standard for NSF was most commonly a retrospective medical review (11 of 16 [68.8%]).

The pooled risk of NSF stratified by group II GBCA is provided in **Figure 3**. The greatest safety margin (ie, largest sample size) was for gadobenate dimeglumine (upper bound 95% CI, 0.12% [0 of 3167]). Upper bound 95% CIs for the other group II GBCAs were 1.11% (0 of 330) for gadobutrol, 0.31% (0 of 1204) for gadoterate meglumine, and 1.59% (0 of 230) for gadoteridol.

The risk-of-bias assessment is summarized in the eTable in the Supplement. Because the incidence of NSF across all studies was 0%, certain factors in the risk-of-bias assessment related to clustering of outcomes at analysis and adjustment for analysis were not applicable. The most common methodological limitation across the included studies was the unblinding of assessors of NSF to the intervention of GBCA administration (15 of 16 studies [94%]). Strengths of all 16 studies included uniformity in the absence of the outcome (NSF) at the start of investigations, consistency in administration of the intervention (GBCA administration) across all groups, and absence of bias between any potential groups in GBCA administration. A potential for funding bias related to industry support was reported in 7 of 16 studies (44%).

Discussion

Across 16 studies and 4931 administrations, we found the pooled risk of NSF from group II GBCAs in patients with stage 4 or 5 CKD to be 0% (upper bound of 95% CI, 0.07%). This finding indicates the per-patient risk of NSF from group II GBCA administration in stage 4 or 5 CKD is likely less than 0.07%. This risk can be compared with the risk of a severe allergic-

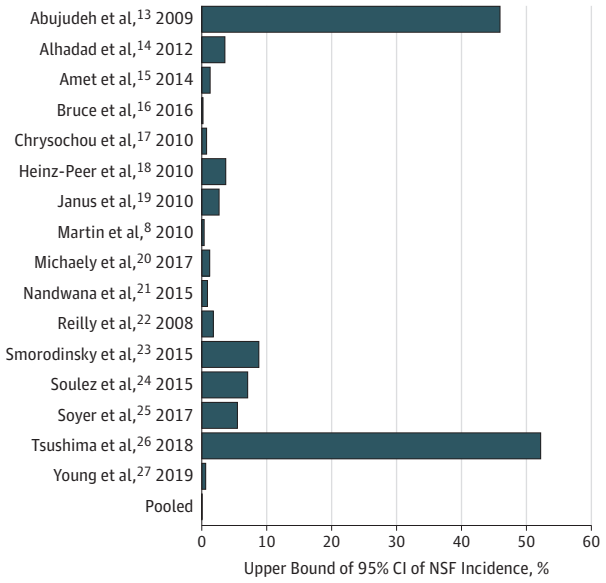
Table 1. Characteristics of Included Studies

Source	Country	Study Type	Study Years	Sites	Mean Age, y	No. Female/Total No. (%)
Abujudeh et al,[13] 2009	United States	Retrospective cohort	2007-2008	Single	72.6 (SD, 9.6)	152/250 (60.8)
Alhadad et al,[14] 2012	Sweden	Retrospective cohort	2001-2008	Single	68 (SD, 14)	146/272 (53.7)
Amet et al,[15] 2014	France	Prospective cohort	2009-2011	Multiple	63 (SD, 14)	Unknown
Bruce et al,[16] 2016	United States	Retrospective cohort	2006-2014	Single	Unknown	Unknown
Chrysochou et al,[17] 2010	United Kingdom	Retrospective cohort	1999-2009	Multiple	60.6 (SD, 15.7)	750/2053 (36.5)
Heinz-Peer et al,[18] 2010	Austria	Retrospective cohort	1997-2007	Single	57.6 (range, 14-91)	79/195 (40.5)
Janus et al,[19] 2010	France	Retrospective cohort	2005-2006	Multiple	59.9 (range, 18-106)	127/308 (41.2)
Martin et al,[8] 2010	United States	Retrospective cohort	2008	Single	51 (range, 17-83)	390/784 (49.7)
Michaely et al,[20] 2017	Multiple	Prospective cohort	2008-2015	Multiple	66.7 (SD, 12.5)	317/908 (34.9)
Nandwana et al,[21] 2015	United States	Retrospective cohort	2010-2014	Single	50 (SD, 13)	172/401 (42.9)
Reilly,[22] 2008	United States	Retrospective cohort	2000-2007	Single	61.8 (SD, 9.8)	2/141 (1.4)
Smorodinsky et al,[23] 2015	United States	Retrospective cohort	2004-2007	Single	53.5 (range, 12-87)	492/1167 (42.2)
Soulez et al,[24] 2015	United States	Prospective cohort	2008-2010	Multiple	63.6 (SD, 13.4)[a]	21/45 (46.7)[a]
					64.8 (SD, 15.9)[b]	4/12 (33.3)[b]
Soyer et al,[25] 2017	Multiple	Prospective cohort	2008-2013	Multiple	49.5 (range, 0-98)	18 850/35 499 (53.1)
Tsushima et al,[26] 2018	Japan	Prospective cohort	2015-2017	Multiple	58.1 (SD, 17.4)	1809/3337 (54.2)
Young et al,[27] 2019	United Kingdom	Retrospective cohort	2004-2016	Single	55.6 (SD, 16.1)	8916/15 377 (58.0)

[a] Indicates cases of gadobenate dimeglumine administration.

[b] Indicates cases of gadoteridol administration.

Figure 2. Incidence and Upper Bound of 95% CI of Nephrogenic Systemic Fibrosis (NSF) in Patients With Stage 4 or 5 Chronic Kidney Disease by Study



The 95% CI data are stratified by 16 studies included in the meta-analysis and represent NSF incidence across all studies (0 of 4931 [0%]). Pooled refers to pooled exposures of all studies.

like contrast reaction, which has been estimated to be approximately 0.04% for modern low-osmolality iodinated contrast agents[33] and approximately 0.006% to 0.02% for group II GBCAs.[34] Despite existing US Food and Drug Administration guidelines indicating that all GBCAs are contraindicated if the eGFR is less than 30 mL/min/1.73 m^2, these data suggest that group II GBCAs are relatively safe in patients with severe CKD, and their benefits may exceed their risks for indicated examinations. Consistent with our results, recent updates to the ACR,[28] European Society of Urogenital Radiology,[29] and Canadian Association of Radiologists[35] guidelines support use of indicated low-risk GBCAs in this setting.

In comparison with the risk of contrast-induced acute kidney injury, these data indicate that, in patients with stage 4 or 5 CKD who are not receiving dialysis, there is a clearer safety profile for contrast-enhanced MRI using a single-dose group II GBCA than there is for contrast-enhanced computed tomography using a single-dose low-osmolality iodinated contrast agent.[28,29,36,37] The number needed to harm from low-osmolality iodinated contrast agents (ie, contrast-induced acute kidney injury) has been estimated to be between 1 in 6 and no harm evident (ie, indicating substantial uncertainty) based on recent large, propensity score-adjusted retrospective cohort studies.[36,37] In both cases (contrast-enhanced computed tomography and contrast-enhanced MRI), the harms of delayed diagnosis and misdiagnosis resulting from the withholding of contrast material in at-risk patients are incompletely measured but likely real.[10] For many disease states, unenhanced imaging has poorer diagnostic accuracy than contrast-enhanced imaging, increasing the risk of diagnostic error and iatrogenic morbidity and mortality.[10]

Group II GBCAs include 3 macrocyclic agents with 100% renal excretion (gadoteridol, gadoterate meglumine, and gadobutrol) and 1 linear ionic agent with approximately 95% renal and 5% hepatobiliary excretion (gadobenate dimeglumine).[28] Of the 4931 administrations we evaluated,

Table 2. Study Characteristics Related to Group II GBCA Administration and NSF

Source	Total Exposures[a]	GBCA	Reason for GBCA Administration	Follow-up		Standard for NSF	Notes/Comments
				Time	Loss		
Abujudeh et al,[13] 2009	6	Gadobenate dimeglumine	Medically necessary	Mean (SD), 3.6 (2.0) mo	None	Medical records and skin/extremity examinations reviewed to identify signs or symptoms of NSF; if no mention, it was assumed the patient did not have NSF	Predominantly patients with stage 3 CKD
Alhadad et al,[14] 2012	101 (11, 85, and 5)	Multiple (gadobenate dimeglumine, gadoterate meglumine, and gadoteridol)	Routine clinical care	Mean (SD), 46.8 (32.4) mo	None	Electronic medical record for study cohort searched for any sign or symptom of NSF after MRI; diagnosis based on skin biopsy histologic findings	Dermopathologic record review of included cases
Amet et al,[15] 2014	280 (12, 11, 255, and 2)	Multiple (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, and gadoteridol)	Routine clinical care	At least 4 mo after administration (specific data unavailable)	7.5% Loss (unclear which cohort)	Patient-reported questionnaire of skin findings and evaluation by nephrologist; if suspected, confirmed with 2 dermatologists and 2-site biopsy	Follow-up of patients undergoing dialysis
Bruce et al,[16] 2016	1423	Gadobenate dimeglumine	Routine clinical practice, protocol to give gadobenate dimeglumine in those with eGFR of <30 mL/min/1.73 m^2	Unknown, follow-up not directly linked to dosing	NA	Institution-wide targeted health care professional survey to assess for known or suspected cases of NSF and annual dermopathologic review for NSF; diagnosis confirmed based on skin biopsy findings	NSF outcome assessed on a time frame basis, not a per-patient basis
Chrysochou et al,[17] 2010	483 (445, 13, and 25)	Multiple (gadobenate dimeglumine, gadobutrol, and gadoterate meglumine)	Routine clinical care	Mean (SD), 28.6 (18.2) mo	NA	Medical records of study cohort evaluated for signs of NSF; any skin biopsy records in patients having received gadolinium were evaluated	2278 Patients spanning stages 3-5 CKD, with multiple agents evaluated
Heinz-Peer et al,[18] 2010	96 (12, 17, 52, and 15)	Multiple (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, and gadoteridol)	Routine clinical care	Unknown	NA	Medical records for study cohort reviewed for documentation of diagnosed NSF or suspected features; histologic findings of any patient with skin biopsy reviewed by dermatologist. Postmortem records reviewed. Diagnosis based on skin biopsy finding or clinical suspicion	Study reports 4 administrations of gadoterate meglumine in confounded cases of NSF
Janus et al,[19] 2010	135	Gadoterate meglumine	Routine clinical care	Within 4 mo of administration (more precise data unavailable)	NA	Medical records evaluated for cutaneous disorders within 4 mo after MRI; patients routinely evaluated by nephrologist during this interval	3 cases of gadobenate exposure; eGFR data unavailable; no cases of NSF within study cohort
Martin et al,[8] 2010	784	Gadobenate dimeglumine	Pretransplant evaluation	Patients included in study if clinical follow-up available 6 mo after last administration; 94%, >10 mo; 6%, 8-10 mo	None	Medical records and dermatopathology records reviewed for all cases in study cohort	All patients had follow-up ≥6 mo
Michaely et al,[20] 2017	284	Gadobutrol	Patients with renal disease requiring contrast-enhanced MRI consented for study inclusion, nonrandomized open label design	Clinical examination at 12 and 24 mo; telephone interviews at 1, 3, 6, and 18 mo after administration	No loss to 2-y record follow-up	Any skin finding of suspected NSF was clinically evaluated; diagnosis based on skin biopsy finding	Analysis stratified by multiple eGFR groups
Nandwana et al,[21] 2015	394	Gadobenate dimeglumine	Routine clinical care	>60 d Required for study inclusion; mean, 37.2 mo	None	Electronic medical records reviewed for NSF or NSF-like symptoms	Study details of patients, not exposures; all patients included had follow-up of 60 d
Reilly,[22] 2008	198	Gadoteridol	Routine clinical care	Patients with <14 d excluded; mean (SD), 18.8 (15.6) mo	None	Medical records for study cohort searched for NSF	Veterans Affairs hospital cohort

(continued)

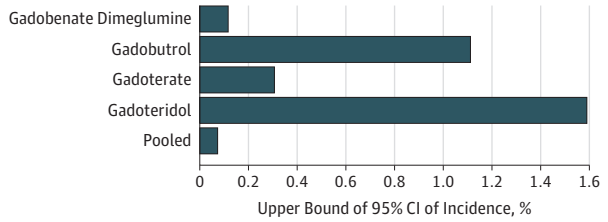
Table 2. Study Characteristics Related to Group II GBCA Administration and NSF (continued)

Source	Total Exposures[a]	GBCA	Reason for GBCA Administration	Follow-up		Standard for NSF	Notes/Comments
				Time	Loss		
Smorodinsky et al,[23] 2015	40	Gadobenate dimeglumine	Routine clinical care for liver disease	Records were considered sufficient for follow-up if 60 d after administration; mean (range), 49.5 mo (61-3400 d)	19.2% of Cohort	All dermatopathology reports in study patients were reviewed for mention of NSF; manual review of the medical records during study time period also performed	Study evaluating primarily patients in hepatology department
Soulez et al,[24] 2015	50 (40 and 10)	Multiple (gadobenate dimeglumine and gadoteridol)	Routine clinical care	Clinic visits to assess for NSF at 12 and 24 mo after administration; telephone follow-up at 18 mo	5 for Gadobenate dimeglumine and 2 for gadoteridol	Any skin finding of suspected NSF was clinically evaluated by a dermatologist; diagnosis based on skin biopsy finding	Study consisted of 2 parallel studies evaluating gadobenate dimeglumine and gadoteridol
Soyer et al,[25] 2017	65	Gadoterate meglumine	Consecutive eligible patients, routine clinical care	≥3 mo from time of administration to physician follow-up survey; mean, 4.9 mo	7.4%, Unclear which eGFR cohorts	Follow-up questionnaire sent to referring physician to evaluate for signs and symptoms of NSF	Extracted data from much larger cohort study of 35 499 patients
Tsushima et al,[26] 2018	5	Gadobutrol	Noninterventional study of consecutive patients receiving gadobutrol for routine clinical care	3-25 mo for Patients with eGFR <30 mL/min/1.73 m^2	None	Unknown	Extracted data from prospective surveillance study of 3337 patients
Young et al,[27] 2019	587	Gadoterate meglumine	Routine clinical care	Mean (SD), 72 (30) mo	NA	Dermatology records searched during study to identify recorded NSF diagnosis after contrast-enhanced MRI	Only nonconfounded GBCA administrations included in study cohort

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GBCA, gadolinium-based contrast agent; MRI, magnetic resonance imaging; NA, not applicable; NSF, nephrogenic systemic fibrosis.

[a] Zero cases of NSF were observed in any of the studies.

Figure 3. Incidence and Upper Bound of 95% CI of Nephrogenic Systemic Fibrosis (NSF) in Patients With Stage 4 or 5 Chronic Kidney Disease by Agent



The 95% CI data are stratified by the 4 gadolinium-based contrast agents included in the study and represent NSF incidence across all studies (0 of 4931 [0%]). Pooled refers to pooled exposures of all agents.

3167 were exposed to gadobenate dimeglumine. Therefore, most of the safety evidence in this setting is for a specific linear ionic group II GBCA with partial hepatobiliary excretion. Hepatobiliary excretion may offer a protective advantage against NSF by providing an alternative clearance mechanism in patients with severely impaired kidney function.

Previous meta-analyses on GBCA and NSF risk have been heavily weighted by group I GBCAs.[1,4] Agarwal et al[1] analyzed 7 studies published from 2006 to 2007 with 4276 patients and found an odds ratio of 26.7 (95% CI, 10.3-69.4) for the risk of NSF. Six of the studies evaluated majority or sole group I GBCA exposure, and 1 study had an unknown exposure history. Zhang et al[4] performed an updated meta-analysis of 11 studies published from 2006 to 2012 with 5405 patients and found an odds ratio of 16.5 (95% CI, 7.5-36.5) for the risk of NSF, suggesting a decline in risk since preventive strategies were introduced. However, because their inclusion criteria required patients diagnosed with NSF, 3 studies of GBCA without evidence of NSF published in 2010, 2013, and 2014 were excluded. Therefore, the existing published meta-analyses[1,4] are likely not directly relevant to the risk of NSF from group II GBCA.

Strengths and Limitations

Some strengths of our analysis include its focus on a specific and clinically important question, narrow inclusion criteria, a comprehensive search strategy, dual inclusion methods with high interrater agreement, and a low risk of bias for most domains. Common weaknesses included general lack of blinding in the included studies, no universal reference standard for the diagnosis of NSF, and insufficient sample size for specific GBCAs. Most of the studies in our cohort (69%) performed retrospective evaluations of the medical records to identify potential cases of NSF, raising the possibility that cases could be missed in situations in which individuals were no longer patients in the system where the MRI was performed. However, most studies provided a minimum follow-up interval for study inclusion and provided mean times for record review follow-

ing GBCA administration (Table 2). In 7 of the studies included in our analysis, development of NSF also was evaluated in patients who received non–group II GBCAs.[8,14-18,23] In 3 of these studies, NSF was observed.[8,16,18] These positive controls suggest the lack of NSF detection within our analysis of group II GBCAs was not due solely to methodological biases.

Although our sample size was large (n = 4931), no NSF events occurred. Therefore, the true risk of NSF in this cohort is unknown. The upper bound of the 95% CI was 0.07%, but this result depended on sample size. The absolute risk could be (for example) nonexistent, 1 in a million, or 1 in 2000. With a larger sample, a more precise estimate would be possible. In addition, the analysis reflects studies performed before and after changes to practice guidelines designed to mitigate NSF risk. Therefore, our results are not a pure reflection of either era. There have been single-digit numbers of reports of unconfounded NSF resulting after exposure to a group II GBCA,[35] suggesting that the risk of NSF in high-risk patients receiving a group II GBCA is not zero. Larger series are needed to determine what that risk is. Our analysis is unable to determine the risk of sequential group II GBCA exposures or the risk from group II GBCA administration in the setting of acute kidney injury. The studies we analyzed did not comprehensively or universally address those issues, and this is an area for future investigation. Our analysis was designed to evaluate harms specifically related to development of NSF. It is not a comprehensive assessment of all potential GBCA-related risk (eg, allergiclike reactions, gadolinium retention).

Current ACR guidelines do not require informed consent before group II GBCA administration.[28] If a practice wishes to do so, we would suggest the following: "Current evidence does not support withholding group II GBCAs on the basis of NSF risk alone in patients with stage 4 or 5 CKD. Although there is likely a very small risk of developing NSF (likely less than 0.07%) in this population, if the diagnostic question necessitates the use of a GBCA, use of a group II GBCA is recommended."

Conclusions

The risk of NSF from group II GBCA administration in patients with stage 4 or 5 CKD is likely less than 0.07%. The harms of withholding group II GBCA for indicated examinations may outweigh the risk of NSF in this population. These data support recent updates to ACR and European Society of Urogenital Radiology guidelines[28,29] liberalizing use of low-risk GBCAs for indicated examinations in this setting.

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Invited Commentary

Risk of Gadolinium-Based Contrast Agents in Chronic Kidney Disease—Is Zero Good Enough?

Saugar Maripuri, MD; Kirsten L. Johansen, MD

In the 1990s and early 2000s, numerous patients with chronic kidney disease (CKD) were exposed to gadolinium-based contrast agents (GBCAs) for contrast-enhanced magnetic resonance imaging (MRI). At the time, the use of GBCAs was considered a safe alternative to iodinated contrast used with computed tomographic scans because the risk of contrast-induced nephropathy could be avoided. During this period, a small number of patients with CKD developed a debilitating skin condition, initially called nephrogenic fibrosing dermopathy, because the most obvious manifestations were diffuse skin thickening and fibrosis. The condition was occasionally severe enough to involve the heart, lungs, liver, and skeletal muscle and was later renamed nephrogenic systemic fibrosis (NSF). Patients with NSF experienced significant morbidity due to irreversible systemic fibrotic changes and higher mortality than patients without NSF.[1]

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Nephrogenic systemic fibrosis was initially a mystery; in 2006, 2 case-control studies[2,3] identified an association between GBCAs and NSF in patients with chronic CKD. The US Food and Drug Administration (FDA) issued an advisory about the association of GBCAs and NSF in 2006[4] and subsequently issued a black box warning in 2007,[5] instructing physicians to avoid the use of all GBCAs in patients at risk for NSF. The pathophysiologic cause of NSF was later confirmed by histopathologic evaluation, which revealed gadolinium deposition in skin biopsy specimens of affected patients. Given that kidney failure greatly increases the elimination half-life of GBCAs, it was postulated that gadolinium ions