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 m²) 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.

TRIAL REGISTRATION PROSPERO identifier: CRD42019123284

Published online December 9, 2019.

© 2019 American Medical Association. All rights reserved.
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 m². After more than 500 cases of NSF were reported from 1997 to 2007, regulations were adopted to prevent NSF. 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. 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. Such recommendations informed hospital policies and were successful in effectively eliminating the disease. 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. In addition, the guidelines were applied to all GBCAs regardless of gadolinium-chelate lability or association with NSF. Accumulating literature and newer guidelines 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 and the European Society of Urogenital Radiology guidelines on contrast agents, version 10.0 recognize differences in risk of NSF between GBCAs and classify GBCAs into 3 distinct (albeit slightly different) groups. 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.” 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.

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.
word 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: 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 non-randomized cohort studies. 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).

---

**Table 1. Characteristics of Included Studies**

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Study Type</th>
<th>Study Years</th>
<th>Sites</th>
<th>Mean Age, y</th>
<th>No. Female/Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abujudeh et al, 1, 2 2009</td>
<td>United States</td>
<td>Retrospective cohort</td>
<td>2007-2008</td>
<td>Single</td>
<td>72.6 (SD, 9.6)</td>
<td>152/250 (60.8)</td>
</tr>
<tr>
<td>Alhadad et al, 3, 4 2012</td>
<td>Sweden</td>
<td>Retrospective cohort</td>
<td>2001-2008</td>
<td>Single</td>
<td>68 (SD, 14)</td>
<td>146/272 (53.7)</td>
</tr>
<tr>
<td>Amet et al, 5, 6 2014</td>
<td>France</td>
<td>Prospective cohort</td>
<td>2009-2011</td>
<td>Multiple</td>
<td>63 (SD, 14)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bruce et al, 7, 8 2016</td>
<td>United States</td>
<td>Retrospective cohort</td>
<td>2006-2014</td>
<td>Single</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Chrysochou et al, 9, 10 2010</td>
<td>United Kingdom</td>
<td>Retrospective cohort</td>
<td>1999-2009</td>
<td>Multiple</td>
<td>60.6 (SD, 15.7)</td>
<td>750/2053 (36.5)</td>
</tr>
<tr>
<td>Heinz-Peer et al, 11 2010</td>
<td>Austria</td>
<td>Retrospective cohort</td>
<td>1997-2007</td>
<td>Single</td>
<td>57.6 (range, 14-91)</td>
<td>79/195 (40.5)</td>
</tr>
<tr>
<td>Janus et al, 12 2010</td>
<td>France</td>
<td>Retrospective cohort</td>
<td>2005-2006</td>
<td>Multiple</td>
<td>59.9 (range, 18-106)</td>
<td>127/308 (41.2)</td>
</tr>
<tr>
<td>Martin et al, 13 2010</td>
<td>United States</td>
<td>Retrospective cohort</td>
<td>2008</td>
<td>Single</td>
<td>51 (range, 17-83)</td>
<td>390/784 (49.7)</td>
</tr>
<tr>
<td>Michaela et al, 14 2017</td>
<td>Multiple</td>
<td>Prospective cohort</td>
<td>2008-2015</td>
<td>Multiple</td>
<td>66.7 (SD, 12.5)</td>
<td>317/908 (34.9)</td>
</tr>
<tr>
<td>Nandwana et al, 15 2015</td>
<td>United States</td>
<td>Retrospective cohort</td>
<td>2010-2014</td>
<td>Single</td>
<td>50 (SD, 13)</td>
<td>172/401 (42.9)</td>
</tr>
<tr>
<td>Reilly, 16 2008</td>
<td>United States</td>
<td>Retrospective cohort</td>
<td>2000-2007</td>
<td>Single</td>
<td>61.8 (SD, 9.8)</td>
<td>2/141 (1.4)</td>
</tr>
<tr>
<td>Smorodinsky et al, 17 2015</td>
<td>United States</td>
<td>Retrospective cohort</td>
<td>2004-2007</td>
<td>Single</td>
<td>53.5 (range, 12-87)</td>
<td>492/1167 (42.2)</td>
</tr>
<tr>
<td>Soulez et al, 18 2015</td>
<td>United States</td>
<td>Prospective cohort</td>
<td>2008-2010</td>
<td>Multiple</td>
<td>63.6 (SD, 13.4)</td>
<td>21/45 (46.7)</td>
</tr>
<tr>
<td>Soyer et al, 19 2017</td>
<td>Multiple</td>
<td>Prospective cohort</td>
<td>2008-2013</td>
<td>Multiple</td>
<td>49.5 (range, 0-98)</td>
<td>18 850/15 499 (53.1)</td>
</tr>
<tr>
<td>Tsushima et al, 20 2018</td>
<td>Japan</td>
<td>Prospective cohort</td>
<td>2015-2017</td>
<td>Multiple</td>
<td>58.1 (SD, 17.4)</td>
<td>1809/3337 (54.2)</td>
</tr>
<tr>
<td>Young et al, 21 2019</td>
<td>United Kingdom</td>
<td>Retrospective cohort</td>
<td>2004-2016</td>
<td>Single</td>
<td>55.6 (SD, 16.1)</td>
<td>8916/15 377 (58.0)</td>
</tr>
</tbody>
</table>

* Indicates cases of gadobenate dimeglumine administration.

b Indicates cases of gadoteridol administration.
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.

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-like contrast reaction, which has been estimated to be approximately 0.04% for modern low-osmolality iodinated contrast agents23 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 m², 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 Radiologists35 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...
Table 2. Study Characteristics Related to Group II GBCA Administration and NSF

<table>
<thead>
<tr>
<th>Source</th>
<th>Total Exposures&lt;sup&gt;a&lt;/sup&gt;</th>
<th>GBCA</th>
<th>Reason for GBCA Administration</th>
<th>Follow-up Time Mean (SD)</th>
<th>Loss</th>
<th>Standard for NSF</th>
<th>Notes/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abujudeh et al,&lt;sup&gt;11&lt;/sup&gt; 2009</td>
<td>6</td>
<td>Gadobenate dimeglumine</td>
<td>Medically necessary</td>
<td>Mean (SD), 3.6 (2.0) mo</td>
<td>None</td>
<td>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</td>
<td>Predominantly patients with stage 3 CKD</td>
</tr>
<tr>
<td>Alhadad et al,&lt;sup&gt;14&lt;/sup&gt; 2012</td>
<td>101 (11, 85, and 5)</td>
<td>Multiple (gadobenate dimeglumine, gadoterate meglumine, and gadodoteridol)</td>
<td>Routine clinical care</td>
<td>Mean (SD), 46.8 (32.4) mo</td>
<td>None</td>
<td>Electronic medical record for study cohort searched for any sign or symptom of NSF after MRI; diagnosis based on skin biopsy histologic findings</td>
<td>Dermopathologic record review of included cases</td>
</tr>
<tr>
<td>Amet et al,&lt;sup&gt;15&lt;/sup&gt; 2014</td>
<td>280 (12, 11, 255, and 2)</td>
<td>Multiple (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, and gadodoteridol)</td>
<td>Routine clinical care</td>
<td>At least 4 mo after administration (specific data unavailable)</td>
<td>7.5% Loss (unclear cohort)</td>
<td>Patient-reported questionnaire of skin findings and evaluation by nephrologist; if suspected, confirmed with 2 dermatologists and 2-site biopsy</td>
<td>Follow-up of patients undergoing dialysis</td>
</tr>
<tr>
<td>Bruce et al,&lt;sup&gt;16&lt;/sup&gt; 2016</td>
<td>1423</td>
<td>Gadobenate dimeglumine</td>
<td>Routine clinical practice, protocol to give gadobenate dimeglumine in those with eGFR of &lt;30 mL/min/1.73 m²</td>
<td>Unknown, follow-up not directly linked to dosing</td>
<td>NA</td>
<td>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</td>
<td>NSF outcome assessed on a time frame basis, not a per-patient basis</td>
</tr>
<tr>
<td>Chrysochou et al,&lt;sup&gt;17&lt;/sup&gt; 2010</td>
<td>483 (445, 13, and 25)</td>
<td>Multiple (gadobenate dimeglumine, gadobutrol, and gadoterate meglumine)</td>
<td>Routine clinical care</td>
<td>Mean (SD), 28.6 (18.2) mo</td>
<td>NA</td>
<td>Medical records of study cohort evaluated for signs of NSF; any skin biopsy records in patients having received gadolinium were evaluated</td>
<td>2278 Patients spanning stages 3–5 CKD, with multiple agents evaluated</td>
</tr>
<tr>
<td>Heinz-Peer et al,&lt;sup&gt;18&lt;/sup&gt; 2010</td>
<td>96 (12, 17, 52, and 15)</td>
<td>Multiple (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, and gadodoteridol)</td>
<td>Routine clinical care</td>
<td>Unknown, follow-up within 4 mo of administration (more precise data unavailable)</td>
<td>NA</td>
<td>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</td>
<td>Study reports 4 administrations of gadoterate meglumine in confounded cases of NSF</td>
</tr>
<tr>
<td>Janus et al,&lt;sup&gt;19&lt;/sup&gt; 2010</td>
<td>135</td>
<td>Gadoterate meglumine</td>
<td>Routine clinical care</td>
<td>Within 4 mo of administration; data unavailable</td>
<td>NA</td>
<td>Medical records evaluated for cutaneous disorders within 4 mo after MRI; patients routinely evaluated by nephrologist during this interval</td>
<td>3 cases of gadobenate exposure; eGFR data unavailable; no cases of NSF within study cohort</td>
</tr>
<tr>
<td>Martin et al,&lt;sup&gt;8&lt;/sup&gt; 2010</td>
<td>784</td>
<td>Gadobenate dimeglumine</td>
<td>Pretransplant evaluation</td>
<td>Patients included in study if clinical follow-up available 6 mo after last administration; 94%, &gt;10 mo; 6%, 8-10 mo</td>
<td>None</td>
<td>Medical records and dermatopathology records reviewed for all cases in study cohort</td>
<td>All patients had follow-up ≥6 mo</td>
</tr>
<tr>
<td>Michaely et al,&lt;sup&gt;20&lt;/sup&gt; 2017</td>
<td>284</td>
<td>Gadobutrol</td>
<td>Patients with renal disease requiring contrast-enhanced MRI consented for study inclusion, nonrandomized open label design</td>
<td>Clinical examination at 12 and 24 mo; telephone interviews at 1, 3, 6, and 18 mo after administration</td>
<td>No loss to 2-y record follow-up</td>
<td>Any skin finding of suspected NSF was clinically evaluated; diagnosis based on skin biopsy finding</td>
<td>Analysis stratified by multiple eGFR groups</td>
</tr>
<tr>
<td>Nandwana et al,&lt;sup&gt;21&lt;/sup&gt; 2015</td>
<td>394</td>
<td>Gadobenate dimeglumine</td>
<td>Routine clinical care</td>
<td>&gt;60 d Required for study inclusion; mean, 37.2 mo</td>
<td>None</td>
<td>Electronic medical records reviewed for NSF or NSF-like symptoms</td>
<td>Study details of patients, not exposures; all patients included had follow-up of 60 d</td>
</tr>
<tr>
<td>Reilly,&lt;sup&gt;22&lt;/sup&gt; 2008</td>
<td>198</td>
<td>Gadoteridol</td>
<td>Routine clinical care</td>
<td>Patients with &lt;14 d excluded; mean (SD), 18.8 (15.6) mo</td>
<td>None</td>
<td>Medical records for study cohort searched for NSF</td>
<td>Veterans Affairs hospital cohort</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Total Exposures</th>
<th>GBCA</th>
<th>Reason for GBCA Administration</th>
<th>Follow-up</th>
<th>Standard for NSF</th>
<th>Notes/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smorodinsky et al.</td>
<td>40</td>
<td>Gadobenate dimeglumine</td>
<td>Routine clinical care for liver disease</td>
<td>Records were considered sufficient for follow-up if 60 d after administration; mean (range), 49.5 mo (61-3400 d)</td>
<td>19.2% of Cohort</td>
<td>All dermatopathology reports in study patients were reviewed for mention of NSF; manual review of the medical records during study time period also performed</td>
</tr>
<tr>
<td>Soulez et al.</td>
<td>50 (40 and 10)</td>
<td>Multiple (gadobenate dimeglumine and gadoteridol)</td>
<td>Routine clinical care</td>
<td>Clinic visits to assess for NSF at 12 and 24 mo after administration; telephone follow-up at 18 mo</td>
<td>5 for Gadobenate dimeglumine and 2 for gadoteridol</td>
<td>Any skin finding of suspected NSF was clinically evaluated by a dermatologist; diagnosis based on skin biopsy finding</td>
</tr>
<tr>
<td>Soyer et al.</td>
<td>65</td>
<td>Gadoterate dimeglumine</td>
<td>Consecutive eligible patients, routine clinical care</td>
<td>≥3 mo from time of administration to physician follow-up survey; mean, 4.9 mo</td>
<td>7.4%, Unclear which eGFR cohorts</td>
<td>Follow-up questionnaire sent to referring physician to evaluate for signs and symptoms of NSF</td>
</tr>
<tr>
<td>Tsuchima et al.</td>
<td>5</td>
<td>Gadobutrol</td>
<td>Noninterventional study of consecutive patients receiving gadobutrol for routine clinical care</td>
<td>3-25 mo for Patients with eGFR &lt;30 mL/min/1.73 m²</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>Young et al.</td>
<td>587</td>
<td>Gadoterate dimeglumine</td>
<td>Routine clinical care</td>
<td>Mean (SD), 72 (30) mo</td>
<td>NA</td>
<td>Dermatology records searched during study to identify recorded NSF diagnosis after contrast-enhanced MRI</td>
</tr>
</tbody>
</table>

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.

* 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.

Gadobenate Dimeglumine
Gadobutrol
Gadoterate dimeglumine
Gadoteridol
Pooled

Upper Bound of 95% CI of Incidence, %

Previous meta-analyses on GBCA and NSF risk have been heavily weighted by group I GBCAs. Agarwal et al 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 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 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 individual patients were not 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 following 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.\textsuperscript{8,14-18,23} In 3 of these studies, NSF was observed.\textsuperscript{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,\textsuperscript{8,14-18,23} 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.\textsuperscript{2,8} 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\textsuperscript{20,29} liberalizing use of low-risk GBCAs for indicated examinations in this setting.
Risk of nephrogenic systemic fibrosis is low in renally insufficient individuals.


Supplementary Online Content


eMethods 1. Complete Search Strategies

eMethods 2. Cohort of 62 Studies Evaluated at Full Manuscript Level by Both Study Team Members

eTable. Risk of Bias Assessment

eReferences.

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods 1: Complete search strategies

Literature Searches

Ovid MEDLINE; Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Daily and Versions
(1462 results on January 29, 2019)

1. exp renal insufficiency, chronic/ or (renal insufficiency/ and (chronic or end-stage or "stage 4" or "stage 5" or stage iv or stage v).tw,kw) or ((chronic or end-stage or "stage 4" or "stage 5" or stage iv or stage v) adj3 (kidney* or renal)).tw,kw or ((kidney* or renal) adj3 (insufficien* or transplant*)).tw,kw or (impaired adj1 (kidney* or renal)).tw,kw or ((egfr or gfr) adj2 "30").tw,kw or exp renal dialysis/ or dialysis/ or (dialysis or hemodialysis or nsf).ti or nephrogenic fibrosing dermopathy/ or (nephrogenic systemic fibrosis or nephrogenic fibrosing dermopath*).tw,kw

2. ((gadolinium/ or gadolinium dtpa/) and contrast media/) or ((contrast or radiocontrast) adj1 (agent* or dye* or material* or media* or medium*)).ti. or (dotarem or gadavist or gadobenate or gadobutrol or gadoteri* or gadolinium or multihance or prohance).tw,kw

3. (and/1-2) not (exp animals/ not humans/)  

Embase.com (1670 results on January 29, 2019)

1. 'chronic kidney failure'/exp OR (((chronic OR 'end stage' OR 'stage iv' OR 'stage v' OR 'stage 4' OR 'stage 5') NEAR/2 (kidney* OR renal)):ti,ab,kw) OR (((kidney* OR renal) NEAR/3 (insufficien* OR transplant*)):ti,ab,kw) OR (impaired NEAR/1 (kidney* OR renal)):ti,ab,kw) OR ((egfr OR gfr) NEAR/1 '30'):ti,ab,kw) OR dialysis:ti OR hemodialysis:ti OR nsf:ti OR nephrogenic systemic fibrosis:ti,ab,kw OR nephrogenic fibrosing dermopathies:ti,ab,kw OR nephrogenic fibrosing dermopathy:ti,ab,kw

2. 'gadoterate meglumine'/exp OR 'gadobenate dimeglumine'/exp OR 'gadobutrol'/exp OR 'gadoteridol'/exp OR 'gadolinium'/exp OR dotarem:ti,ab,kw OR gadavist:ti,ab,kw OR gadobenate:ti,ab,kw OR gadobutrol:ti,ab,kw OR gadoteri*:ti,ab,kw OR gadolinium:ti,ab,kw OR multihance:ti,ab,kw OR prohance:ti,ab,kw

3. #1 AND #2 NOT ('animal'/exp NOT 'human'/de)

Wiley Cochrane Central Register of Controlled Trials (132 results on January 29, 2019)

1. [mh "renal insufficiency, chronic"] or ([mh "renal insufficiency"] and (chronic or "end-stage" or "stage 4" or "stage 5" or "stage iv" or "stage v"):ti,ab) or ((chronic or "end-stage" or "stage 4" or "stage 5" or "stage iv" or "stage v") near/3 (kidney* or renal)):ti,ab or ((kidney* or renal) near/3 (insufficien* or transplant*)):ti,ab or (impaired near/1 (kidney* or renal)):ti,ab or ((egfr or gfr) near/2 "30"):ti,ab or [mh "renal dialysis"] or [mh dialysis] or (dialysis or hemodialysis or nsf):ti or [mh "nephrogenic fibrosing dermopathy"] or ("nephrogenic systemic fibrosis" or "nephrogenic fibrosing dermopathies" or "nephrogenic fibrosing dermopathy"):ti,ab
2. ([mh gadolinium] or [mh "gadolinium dtpa"]) or ((contrast or radiocontrast) near/1 (agent* or dye* or material* or media* or medium*)):ti or (dotarem or gadavist or gadobenate or gadobutrol or gadoteri* or gadolinium or multihance or prohance):ti,ab

3. #1 and #2

**Clarivate Web of Science** (836 results on January 29, 2019)

1. TS=(dotarem OR gadavist OR gadobenate OR gadobutrol OR gadoteri* OR multihance OR prohance) OR TS=(gadolinium NEAR/2 contrast*)

2. TS=((chronic OR "end-stage" OR "stage 4" OR "stage 5" OR "stage iv" OR "stage v") NEAR/2 (kidney* or renal)) OR TS=((kidney* OR renal) NEAR/2 (insufficien* OR transplant*)) OR TS=(impaired NEAR/1 (kidney* OR renal)) OR TS=((egfr OR gfr) NEAR/1 "30") OR TI=(dialysis OR hemodialysis OR NSF) OR TS=("nephrogenic systemic fibrosis" OR "nephrogenic fibrosing dermopathies" OR "nephrogenic fibrosing dermopathy")

3. #2 AND #1 NOT TI=(animal* OR bovine OR cattle OR mice OR mouse OR pig OR pigs OR rabbit* OR rat OR rats)

**Open Grey** (8 results on January 29, 2019)

(dotarem OR gadavist OR gadobenate OR gadobutrol OR gadoteri* OR gadolinium OR multihance OR prohance) AND (chronic OR dialysis OR "end stage" OR nephrogenic OR "stage 4" OR "stage 5" OR "stage iv" OR "stage v")
eMethods 2: Cohort of 62 studies evaluated at full manuscript level by both study team members.


© 2019 American Medical Association. All rights reserved.


T. Ishiguchi, S. Takahashi. Safety of gadoterate meglumine (Gd-DOTA) as a contrast agent for magnetic resonance imaging: results of a post-marketing surveillance study in Japan. Drugs in R & D. 2010. 10:133-45


© 2019 American Medical Association. All rights reserved.


© 2019 American Medical Association. All rights reserved.


L. K. Young, S. Z. Matthew, J. G. Houston. Absence of potential gadolinium toxicity symptoms following 22,897 gadoteric acid (Dotarem) examinations, including 3,209 performed on renally insufficient individuals. European Radiology. 2018. 01:01


T. R. Elmholdt, B. Jorgensen, M. Ramsing, M. Pedersen, A. B. Olesen. Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gadobutrol. NDT Plus. 2010. 3:285-287


Table 1. Risk of bias assessment

<table>
<thead>
<tr>
<th>Author *</th>
<th>ROB1</th>
<th>ROB2</th>
<th>ROB3a</th>
<th>ROB3b</th>
<th>ROB4</th>
<th>ROB5</th>
<th>ROB6</th>
<th>ROB7</th>
<th>ROB8</th>
<th>ROB9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abujudeh HH, et al. (1)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Alhadad A, et al. (2)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Amet S, et al. (3)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bruce R, et al. (4)</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chrysochou C, et al. (5)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heinz-Peer G, et al. (6)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Janus N, et al. (7)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Martin DR et al. (8)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Michaely HJ, et al. (9)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>No. Funded by Bayer Pharma AG.</td>
</tr>
<tr>
<td>Nandwana SB, et al. (10)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reilly RF, (11)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Smorodinsky E, et al. (12)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>No. At least partial funding from Bracco Group.</td>
</tr>
<tr>
<td>Soulez G, et al. (13)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>No. Sponsored by Bracco Diagnostics.</td>
</tr>
<tr>
<td>Soyer P, et al. (14)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tsushima Y, et al. (15)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>No. Funded by Bayer Yakuhin, Ltd.</td>
</tr>
<tr>
<td>Young LK, et al. (16)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table legend:
“Yes”: bias is unlikely to be present; “No”: bias is likely to be present; “N/A”: inadequate information or inapplicable to study design
ROB1, Is the outcome absent at the start of the study?
ROB2, Was clustering at the group level accounted for in analyses?
ROB3a., Were the outcome assessors (for the primary outcome) blind to the intervention?
ROB3b., Was the outcome measurement performed in the same manner with similar intensity in the groups being compared?
ROB4, Was a similarly trained individual administering the intervention across groups?
ROB5, Was the outcome measurement performed in the same manner with similar intensity in the groups being compared?
ROB6, Were the groups similar at baseline?
ROB7, Did the authors perform analyses adjusting for known confounders?
ROB8, Were all the withdrawals described?
ROB9, Is the study free of potential funding bias?
eReferences.


