

Risk of Nephrogenic Systemic Fibrosis after Exposure to Newer Gadolinium Agents

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Prepared by:

Evidence Synthesis Program (ESP) Center
Durham VA Healthcare System
Durham, NC
Karen M. Goldstein, MD, MSPH, Co-Director
Jennifer M. Gierisch, PhD, MPH, Co-Director

Authors:

Principal Investigators:

Karen M. Goldstein, MD, MSPH
Joseph Lunyera, MBChB, MSc

Co-Investigators:

Dinushika Mohottige, MD, MPH
Anastasia-Stefania Alexopoulos, MBBS
Hilary Campbell, PharmD, JD
C. Blake Cameron, MD, MBI
Nicole Sagalla, MD
Timothy J. Amrhein, MD
Matthew J. Crowley, MD, MHS
Jessee R. Dietch, PhD, MS
Adelaide M. Gordon, MPH
Andrzej S. Kosinski, PhD
Sarah Cantrell, MLIS
John W. Williams Jr, MD MHS
Jennifer M. Gierisch, PhD, MPH

Research Associates:

Belinda Ear, MPH
Robyn E. Fortman, BA
Avishek Nagi, MS
Christiana O. Oshotse, BA
Liz Wing, MA



U.S. Department of Veterans Affairs

Veterans Health Administration
Health Services Research & Development Service



PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the [program website](#).

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Patrick Pun, Medical Director, Dialysis Unit, Durham VA Medical Center, for the purpose of guiding the Nephrology Field Advisory Committee's recommendations for development of national and local policies. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

Patrick Pun, MD, MHS
VHA Renal Field Advisory Committee
Medical Director, Dialysis Unit
Durham VA Medical Center

Susan Crowley, MD, FASN
VHA National Program Director for Kidney Disease
Chief, Renal Section
VA Connecticut Healthcare System

Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Brent Wagner, MD, MS, FACP, FASN
Acting Associate Chief of Staff, Research
New Mexico VA Health Care System
Associate Professor of Medicine
University of New Mexico

Clare Haystead, MD
Radiologist, Radiology Service
Durham, VA Medical Center
Assistant Professor of Radiology
Duke University

Roger Chou, MD

Director of the Pacific Northwest Evidence-based Practice Center
Professor of Medicine
Oregon Health & Science University

Ira Krefting, MD

Deputy Director for Safety
Division Medical Imaging Products
Office of Drug Evaluation
US Food and Drug Administration

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

EXECUTIVE SUMMARY

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) is a debilitating and, in most cases, fatal condition associated with exposure to certain gadolinium-based contrast agents (GBCA) administered during magnetic resonance imaging (MRI) or angiography (MRA) scans. Clinically, NSF presents as fibrosis of the skin and internal organs such as the heart, liver, and lungs, and occurs conspicuously in persons with end-stage renal disease (ESRD). The first reports of NSF occurred in the early 2000s, and recognition of a causative relationship between NSF and some GBCAs led to the issuance of an FDA boxed warning in 2007.

Gadolinium remains an optimal contrast agent for the enhancement of MRIs. Because gadolinium is toxic in its free form, it must be stabilized by chelation, or bonding, to a ligand to be safe for human use. GBCAs can be characterized by the structure of their individual chelate (macrocyclic/linear) and charge (ionic/non-ionic). These features contribute to the stability of a given GBCA and how easily gadolinium is disconnected from its ligand. These differences in stability of the linkage of gadolinium to the chelate ligand are thought to be a key factor in the risk of NSF as fibrosis development is thought to be due to gadolinium deposition in tissue. Newer GBCAs impart greater stability to the gadolinium-ligand bond and thus are thought to be associated with lower, or potentially minimal, NSF risk.

An additional critical risk factor for the development of NSF is renal impairment. All GBCAs are cleared, at least in part, from the body by the kidneys, and almost all cases of NSF have occurred in individuals with advanced kidney disease ($eGFR < 30 \text{ mL/min}/1.73\text{m}^2$). However, other patient-level risk factors have been proposed as well, including the severity and chronicity of kidney dysfunction and inflammation.

While some advisory boards recommend liberalized use of the newer classes of GBCAs, others warn against risk for NSF with all classes of GBCAs. These divergent positions reflect uncertainties regarding the relative safety of newer versus older classes of GBCAs and the degree of kidney dysfunction that portends risk for NSF. In the VA, the use of gadolinium is currently restricted in Veterans with advanced kidney disease. These restrictions limit access to high-quality MRI for the diagnosis and management of numerous, and some life-threatening, diseases. Despite these uncertainties, few studies have assessed risk for NSF with GBCA exposure specifically in relation to newer agents; across the range of kidney function; and according to patients' underlying profile on comorbid factors that might amplify NSF risk, including diabetes and hypertension. Thus, synthesizing the existing evidence about the safety profile of newer, and presumably more stable, GBCAs across the spectrum of kidney function could inform clinical policies.

The goal of this report is to provide a systematic review of the existing evidence on the risk of NSF with use of newer GBCAs, specifically American College of Radiology (ACR) group II and III agents, to inform the development of VA guidelines on their use.

At the request of the Veterans Affairs (VA) Nephrology Field Advisory Committee, we conducted a systematic review to address the following key questions (KQ):

KQ 1: When exposed to newer gadolinium-based contrast agents (defined as American College of Radiology group II and III agents), what is the occurrence of nephrogenic systemic fibrosis per index GBCA exposure among:

- A. All patients without restriction by kidney function
- B. Patients with key risk factors for chronic kidney disease (*eg*, diabetes and hypertension)
- C. Patients with any degree of kidney disease (*ie*, acute kidney injury or chronic kidney disease)

KQ 2: When compared with older gadolinium-based contrast agents (American College of Radiology group I agents), what is the occurrence of nephrogenic systemic fibrosis per index GBCA exposure for newer GBCAs among:

- A. All patients without restriction by kidney function
- B. Patients with key risk factors for chronic kidney disease (*eg*, diabetes and hypertension)
- C. Patients with any degree of kidney disease (*ie*, acute kidney injury or chronic kidney disease)

METHODS

We developed and followed a standard protocol for this review in collaboration with operational partners and a Technical Expert Panel (PROSPERO registration number CRD42019135783).

Data Sources and Searches

We searched MEDLINE® (via PubMed®), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from inception through January 7, 2019. We also examined the bibliographies of recent reviews for additional relevant studies.

Study Selection

In brief, the major eligibility criteria were studies that examined ACR group II and/or III GBCA exposure and NSF as an outcome. For ease of clinical applicability, we adopted the class groupings for GBCAs given by the American College of Radiology in their 2018 guidelines. We included a broad range of study designs ranging from nonrandomized trials to cohort studies in order to capture any study quantitatively reporting NSF in association with GBCA exposure at the specific agent level. Studies were excluded if they did not report the number of patients exposed by specific GBCA. Similarly, studies were excluded if they only identified the specific GBCA exposure for those patients ultimately diagnosed with NSF but not the rest of the study population. We also included case reports and case series for patients with NSF that clearly described exposure to an ACR group II and/or III GBCA.

Using these prespecified inclusion/exclusion criteria, investigators and the DistillerSR Artificial Intelligence tool evaluated titles and abstracts to identify potentially eligible studies. Studies that met all eligibility criteria at full-text review were included for data abstraction.

Data Abstraction and Quality Assessment

Key characteristics abstracted included patient descriptors, specifics of gadolinium agent exposure (*eg*, specific agent, dose, number of doses received), comparator (if any), outcomes (confirmed or suspected diagnosis of nephrogenic systemic fibrosis), and source of study funding. Multiple reports from a single study were treated as a single data point, prioritizing results based on the most complete and appropriately analyzed data. Key features relevant to applicability included the match between the sample and target populations (*eg*, age, Veteran status).

For randomized, nonrandomized, and controlled before-after studies, we used criteria from the Cochrane EPOC risk of bias (ROB) tool. We assigned a summary ROB score (low, unclear, high) to individual studies, based on the impact of sources of bias on the results of the study.

For observational cohort and case-control studies, we adapted the Newcastle-Ottawa ROB scale (from the version modified by Guyatt and colleagues). For questions relevant to cohort studies with exposed and non-exposed groups, we consider “exposed” to mean patients who received any ACR Group II or III agent of interest and “nonexposed” to mean patients who received an agent not of primary interest (*eg*, ACR Group I agents). For cohorts that only report an exposed group, we included a “not applicable” response option for questions specific to exposed and nonexposed groups. Given the number of eligible cohort and case-control studies, we did not evaluate the ROB for case reports or case series studies.

Data Synthesis and Analysis

We described the included studies using summary tables and graphical displays. Given the heterogeneity in study methodology, including population enrolled, follow-up time period, and diagnostic criteria, we did not calculate summary effects (*ie*, meta-analysis). As a result, the data were synthesized narratively. While we did not calculate summary estimates across studies, we do present forest plots of the point estimates and exact upper 95% confidence interval (CI) for individual studies that were primarily designed to identify cases of NSF. Studies were grouped by the following categories of kidney function: all patients without restriction by renal function, patients with risk factors for chronic kidney disease, and patients with any degree of kidney disease. This last category was subdivided by stage of kidney disease (*ie*, chronic kidney disease [CKD], as acute kidney injury [AKI] was inconsistently reported). We use the phrase “index GBCA exposure” to refer to the contrast agent of primary exposure as identified in each study.

We analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions. The certainty of evidence (COE) for each key question was assessed using the approach described by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group. We limited GRADE ratings to those outcomes identified by the stakeholders and technical expert panel as critical to decision-making (*ie*, development of NSF). Additionally, we limited COE assessment to the highest order study designs (*ie*, EPOC criteria studies,

prospective and retrospective cohorts). COE was not assessed for studies that only enrolled patients with chronic liver disease.

RESULTS

Results of Literature Search

We identified 1,150 citations, of which 314 were reviewed at the full-text stage. Of these, 28 unique studies were retained for data abstraction. They consisted of 26 cohort studies (10 prospective and 16 retrospective), 1 case control study, and 1 nonrandomized trial.

Because of the variability in methods across included studies and the low numbers NSF cases found, we report the occurrence of NSF cases per index GBCA exposure as opposed to a relative risk, prevalence, or incidence. This allows for accurate reporting of the phenomena of interest and for comparison across studies that use both the term incidence and prevalence. We use the term ‘index’ exposure to indicate the only gadolinium contrast agent exposure as reported by the study or the primary exposure for studies in which patients were exposed to multiple GBCAs (*ie*, confounded exposures).

Summary of Results for Key Questions

KQ 1

There were 16 studies that assessed NSF occurrence following exposure to ACR groups II and III GBCAs; 15 were cohort studies and 1 was a nonrandomized controlled trial. Overall, none of the 16 studies ($n=80,715$) reported a case of NSF during follow up. Three cohort studies enrolled 62,544 patients without restriction for kidney function or CKD risk factors (KQ 1A). No cases of NSF were reported (calculated exact upper 95% confidence interval [CI] range 0.0001 to 0.0011), although the certainty of evidence (COE) is low. There were no studies that assessed NSF risk specifically in patients with key risk factors for CKD such as diabetes and hypertension (KQ 1B). 12 studies assessed rates of NSF in patients with some degree of kidney disease (KQ 1C). Two of these studies, comprising 15,377 and 908 patient-level exposures respectively, reported no cases of NSF among patients with any stage of CKD (calculated exact upper 95% CI range 0.0002 to 0.0196), although rated as low COE. Six studies assessed NSF risk in patients with moderate CKD (stages 3 to 5); 3 of which reported NSF as a primary outcome. These 4 cohort studies had a pooled patient population of 887 and reported no cases of NSF (calculated exact upper 95% CI range 0.0111 to 0.0246), with very low COE. The other three of the 6 studies (2 cohort and 1 nonrandomized controlled trial) assessed NSF as the secondary outcome among a total of 126 index exposures among patients with moderate CKD; none reported cases of NSF. Three studies determined rates of NSF in patients with end-stage renal disease (ESRD): there were no cases of NSF reported among a total of 552 exposed patients across these studies (calculated exact upper 95% CI range 0.0092 to 0.3085) and rated as low COE.

KQ 2

Of the studies that met our inclusion criteria, 12 assessed NSF risk both among patients who had index exposure to ACR group I agents and patients who had index exposure to ACR group II agents. Across the 12 studies, there were 110,345 patients with index exposures to an ACR group I agent, 8,499 patients with index exposures to an ACR group II agent, and no patients with an index exposure to ACR group III GBCAs. Secondary GBCA exposure appears to be an

occurrence in a minority of cases; however, potential GBCA exposure other than the index exposure was not consistently reported across included studies. Overall, there were 41 NSF cases reported with a clearly identified GBCA exposure. Of these NSF cases, 37 occurred after at least some exposure (index or otherwise) to an ACR group I agent and 4 had an index exposure to an ACR group II agent. Of the 4 cases of NSF after index exposure to ACR group II agents, 3 appear to be confounded with other unspecified GBCAs. Two cohort studies in a general patient population (KQ 2A) reported 14 cases of NSF after 108,790 ACR group I exposures (calculated exact upper 95% CI range 0.0001 to 0.0003) and 1 case of NSF after 3,646 ACR group II GBCA exposures (calculated exact upper 95% CI range 0.0018 to 0.0058), although rated as very low COE. Similar to KQ 1, we did not find any studies that focused specifically on patients at risk for CKD (KQ 2B). Across 9 cohort studies that enrolled patients with any degree of kidney disease, including ESRD on dialysis (KQ 2C), 15 cases of NSF were reported after ACR group I GBCA exposure (calculated exact upper 95% CI range 0.0065 to 0.4593), and 0 cases NSF after ACR group II GBCA exposure (calculated exact upper 95% CI range 0.0025 to 0.9750). One additional case was reported among 38 patients on hemodialysis who was exposed to both an ACR group I and group II GBCA (no exact 95% CI calculated for this study). However, the evidence was rated as very low COE. One case-control study that enrolled patients with kidney disease reported 7 patients with NSF after ACR group I index GBCA exposure and 3 after ACR group II index GBCA exposure.

DISCUSSION

Key Findings

The primary objective of KQ 1 was to identify the occurrence of NSF following index exposure to the macrocyclic and newer linear GBCAs (ACR groups II and III). Our secondary objective was to identify the occurrence of NSF within specific subpopulations: all patients regardless of kidney function status; patients with CKD risk factors such as hypertension and diabetes; and patients with any degree of kidney disease. We included 16 eligible studies consisting of 15 cohort studies, and 1 nonrandomized controlled trial. Across these studies, ROB was mostly high or unclear. The pooled patient population in the mostly prospective cohort studies was 80,932. Across these studies, there were no cases of NSF reported following exposure to the macrocyclic and newer linear GBCAs (ACR group II and III). While these findings were consistent across patient subpopulations, the majority of patients exposed across all 16 studies did not have CKD. None of the included studies assessed NSF occurrence specifically among patients with CKD risk factors such as hypertension and diabetes, and AKI was inconsistently reported. The exact calculated upper 95% CI for the estimate of NSF occurrence per exposure ranged from 0.0001 to 0.3085. Thus, rare events remain possible in understudied populations (*eg*, CKD, AKI, and patients at risk for CKD).

We also assessed the occurrence of NSF among patients after index exposure to macrocyclic or newer linear GBCAs (ACR group II or III) compared with older linear GBCAs (ACR group I). We conducted a narrative synthesis of the 12 included studies for KQ 2, including 1 nested case-control study and 11 cohort studies. Across these studies, there were 110,345 patient index exposures to ACR group I GBCAs, 8,499 patient index exposures to ACR group II GBCAs, and no patient index exposures to the single ACR group III GBCA, gadoxetic acid. Most cohort studies were retrospective and reviewed existing chart records and administrative databases with occasional supplementation by provider recall. The majority of the patient-level index exposures

across these 12 studies occurred in general patient populations with mostly normal kidney function (112,436 of 118,844, or 94.6%). Those studies focused on patients with CKD were grouped by general stage of CKD with 3 studies looking at NSF across any CKD stage, 2 studies focused on patients with stage 3-5 CKD, and 4 studies examining patients on dialysis only (5,427 patient index GBCA exposures). No studies specifically examined patients at risk for CKD.

Of the 41 cases of NSF identified with a clearly identified GBCA exposure in these 12 studies, only 4 cases were among ACR group II agents, of which 3 appear to be confounded with other unspecified GBCAs. The rest of the NSF cases occurred among patients with at least some reported exposure to ACR group I agents. Among the 4 cases of NSF that occurred after index exposure to ACR group II agents, all had CKD of some stage and 2 had eGFR <30 or were on dialysis. Thus, across studies with 8,499 index exposures to ACR group II patients there was 1 reported unconfounded case of NSF (note that this case came from a study that did not report exposures received outside the study institution). The exact upper 95% CI for NSF occurrence per index GBCA exposure for ACR group I agents ranged from 0.0001 to 0.4593 compared to ACR group II agents which ranged from 0.0018 to 0.9750. Thus, incident NSF is rare but the confidence intervals for ACR group I and group II agents are similar.

Overall, the relatively scarce data among patients with CKD, those at risk for CKD, and those exposed to the single ACR group III agent limit conclusions that can be drawn about the safety of GBCA exposure in these situations. The certainty of evidence for both KQs was low to very low.

Applicability

Because the currently recognized major determining factors in the pathophysiology of NSF are biological in nature, the results in this report are presumed to be readily applicable to the VA population. In fact, we purposely chose to make eligible those studies that included pediatric populations as we felt that the pathophysiology of NSF would be similar enough to adult populations to provide useful evidence. However, we did find 1 study conducted solely in a VA setting.

Research Gaps/Future Research

In brief, research is needed with patients who have known risk factors for CKD and AKI. Consistent use of standardized categorizations of CKD stages and diagnostic criteria for NSF would strengthen future research findings. Research is also needed on understudied GBCAs, specifically gadodiamide (Omniscan®) and gadopentetate dimeglumine (Magnevist®). Future studies of NSF after GBCA exposure should collect and report detailed exposure history at the individual level, including dose per scan and total cumulative dose per patient. GBCA use must be considered across health care systems to capture comprehensive exposure data. Large, comprehensive health care systems, like the VA, are well-situated to conduct high-quality observational studies that could capture the majority or all GBCA exposures and cases of NSF. In particular, leveraging comprehensive electronic health record systems could support examination of NSF risk among patients with risk factors for CKD and those with AKI who have not been studied to date.

Conclusions

Nephrogenic systemic fibrosis is a rare but devastating and usually lethal disease occurring in patients who have had GBCA exposure. Over the last decade, incidence of NSF dropped off dramatically after formal restrictions limited the use of older linear GBCAs, particularly in patients with advanced kidney disease. However, patients with CKD and their providers need evidence to guide shared decision-making about the use of newer and seemingly safer GBCAs, when MRIs are warranted for clinical care. We found very few cases of NSF reported after index exposures to newer linear and macrocyclic GBCAs. Most reported cases are of uncertain value since they occurred in patients who had also been exposed to other—often older—GBCAs around the same time. Generally, we found little data to inform the care of patients who are at risk for developing CKD or those with AKI. In addition, most GBCA exposures occurred among patients with normal kidney function, and rare cases of NSF cannot be excluded in patients with significant kidney disease.

ABBREVIATIONS

ACR	American College of Radiology
AI	Artificial intelligence
AKI	Acute kidney injury
CI	Confidence interval
CKD	Chronic kidney disease
COE	Certainty of evidence
eGFR	Estimated glomerular filtration rate
ESP	Evidence Synthesis Program
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GBCA	Gadolinium-based contrast agent
HD	Hemodialysis
HSR&D	Health Services Research & Development
KQ	Key question
MD	Mean difference
MeSH	Medical Subject Heading
GBCA	Gadolinium-based contrast agent
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NFD	Nephrogenic fibrosing dermopathy
NSF	Nephrogenic systemic fibrosis
PD	Peritoneal dialysis
PICOTS	Population, intervention, comparator, outcome, timing, and setting
PTH	Parathyroid hormone
RCT	Randomized controlled trial
ROB	Risk of bias
TEP	Technical Expert Panel
VA	Veterans Affairs
VHA	Veterans Health Administration