

Henry Ford Health

Henry Ford Health Scholarly Commons

Nephrology Articles

Nephrology

11-10-2020

Use of Intravenous Gadolinium-based Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation

Jeffrey C. Weinreb

Roger A. Rodby

Jerry Yee

Henry Ford Health, JYEE1@hfhs.org

Carolyn L. Wang

Derek Fine

See next page for additional authors

Follow this and additional works at: https://scholarlycommons.henryford.com/nephrology_articles

Recommended Citation

Weinreb JC, Rodby RA, Yee J, Wang CL, Fine D, McDonald RJ, Perazella MA, Dillman JR, and Davenport MS. Use of Intravenous Gadolinium-based Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. Radiology 2020.

This Article is brought to you for free and open access by the Nephrology at Henry Ford Health Scholarly Commons. It has been accepted for inclusion in Nephrology Articles by an authorized administrator of Henry Ford Health Scholarly Commons.

Authors


Jeffrey C. Weinreb, Roger A. Rodby, Jerry Yee, Carolyn L. Wang, Derek Fine, Robert J. McDonald, Mark A. Perazella, Jonathan R. Dillman, and Matthew S. Davenport

Use of Intravenous Gadolinium-based Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation

Jeffrey C. Weinreb, MD • Roger A. Rodby, MD • Jerry Yee, MD • Carolyn L. Wang, MD • Derek Fine, MD • Robert J. McDonald, MD, PhD • Mark A. Perazella, MD • Jonathan R. Dillman, MD, MS • Matthew S. Davenport, MD

From the American College of Radiology, Reston, Va (J.C.W., C.L.W., R.J.M., J.R.D., M.S.D.); National Kidney Foundation, New York, NY (R.A.R., J.Y., D.F., M.A.P.); Department of Radiology and Biomedical Imaging (J.C.W.) and Department of Internal Medicine, Section of Nephrology (M.A.P.), Yale University School of Medicine, New Haven, Conn; Department of Nephrology, Rush University Medical Center, Chicago, Ill (R.A.R.); Department of Nephrology, Henry Ford Health System, Detroit, Mich (J.Y.); Department of Radiology, University of Washington, Seattle, Wash (C.L.W.); Department of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Md (D.F.); Department of Radiology, Mayo Clinic, Rochester, Minn (R.J.M.); Department of Radiology, Cincinnati Children's Hospital Medical Center at University of Cincinnati College of Medicine, Cincinnati, Ohio (J.R.D.); Departments of Radiology (M.S.D.) and Urology (M.S.D.), Michigan Medicine, 1500 E Medical Center Dr, Room B2 A209B, Ann Arbor, MI 48109-5030; and Michigan Radiology Quality Collaborative, Ann Arbor, Mich (M.S.D.). Received June 28, 2020; revision requested July 20; final revision received September 9; accepted September 11. Address correspondence to M.S.D. (e-mail: matdaven@med.umich.edu).

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

Radiology 2020; 00:1–8 • <https://doi.org/10.1148/radiol.2020202903> • Content codes: 

Inaugural consensus statements were developed and endorsed by the American College of Radiology (ACR) and the National Kidney Foundation to improve and standardize the care of patients with kidney disease who have indication(s) to receive ACR-designated group II or group III intravenous gadolinium-based contrast media (GBCM). The risk of nephrogenic systemic fibrosis (NSF) from group II GBCM in patients with advanced kidney disease is thought to be very low (zero events following 4931 administrations to patients with estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m²; upper bounds of the 95% confidence intervals: 0.07% overall, 0.2% for stage 5D chronic kidney disease [CKD], 0.5% for stage 5 CKD and no dialysis). No unconfounded cases of NSF have been reported for the only available group III GBCM (gadoxetate disodium). Depending on the clinical indication, the potential harms of delaying or withholding group II or group III GBCM for an MRI in a patient with acute kidney injury or eGFR less than 30 mL/min per 1.73 m² should be balanced against and may outweigh the risk of NSF. Dialysis initiation or alteration is likely unnecessary based on group II or group III GBCM administration.

This article is a simultaneous joint publication in *Radiology* and *Kidney Medicine*. The articles are identical except for stylistic changes in keeping with each journal's style. Either version may be used in citing this article.

© 2020 RSNA and the National Kidney Foundation published by Elsevier Inc. This is an open access article under the CC BY NC-ND license.

It is estimated that approximately 50 million doses of gadolinium-based contrast media (GBCM; also known as gadolinium-based contrast agents or GBCAs) are injected annually, and that since 1988 more than 500 million doses have been administered worldwide, comprising approximately one-third of MRI examinations (1,2). While GBCM-enhanced MRI examinations are preferred over unenhanced examinations for many indications, they may be delayed or denied in patients with impaired kidney function due to concerns of adverse events, including nephrogenic systemic fibrosis (NSF) and nephrotoxicity. However, recommendations about the use of GBCM in patients with kidney disease have evolved and have been inconsistent in clinical practice among radiologists and nephrologists, even within the same institution (3).

A multidisciplinary group of five radiologists (J.C.W., C.L.W., R.J.M., J.R.D., M.S.D.) and four nephrologists (R.A.R., J.Y., D.F., M.A.P.) was convened by the American College of Radiology (ACR) and the National Kidney Foundation (NKF), with the intention of improving and standardizing the care of patients with

impaired kidney function who have indication(s) to receive intravenous GBCM. Participants were selected based on known expertise and interest in the subject. Although these statements are based on a combination of the most current scientific evidence and expert consensus opinion, it is important to recognize that in clinical practice, decisions to administer GBCM may not be based on a single consideration (eg, risk of an adverse event specifically related to kidney impairment) but instead are influenced by many factors (eg, probability and necessity of an accurate diagnosis, alternative methods of diagnosis, risks of delayed or misdiagnosis, comorbidities, expectations regarding kidney function recovery, and the risk of an allergic-like reaction). Consequently, recommendations in this document should be considered in the context of the entire clinical scenario.

Conditions purported to be associated with gadolinium retention following GBCM administration are not addressed in this document because they are described irrespective of kidney function or particular GBCM. The clinical significance of retained gadolinium in humans is incompletely characterized (2).

Abbreviations

ACR = American College of Radiology, AKI = acute kidney injury, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, GBCM = gadolinium-based contrast media, NKF = National Kidney Foundation, NSF = nephrogenic systemic fibrosis

Summary

Since the risk of nephrogenic systemic fibrosis is so low with group II gadolinium-based contrast media (GBCM), the potential harms of delaying or withholding group II GBCM for an MRI in a patient with acute kidney injury or estimated glomerular filtration rate less than 30 mL/min per 1.73m² is likely to outweigh the risk in most clinical situations.

Nomenclature

Acute Kidney Injury and Chronic Kidney Disease

Recommended definitions pertaining to intravenous contrast media administration for acute kidney injury (AKI), chronic kidney disease (CKD), contrast-induced acute kidney injury, and contrast-associated acute kidney injury are provided in a previously published ACR-NKF consensus document on intravenous iodinated contrast media (4).

Background

Gadolinium and GBCM

Gadolinium, a rare earth metal in the lanthanide series of the periodic table, has been used in most MRI intravenous contrast media because it is strongly paramagnetic, thereby altering the relaxation of water in such a way that it may permit discrimination between normal and abnormal tissues in humans. However, “free” gadolinium from salts such as trichloride is toxic due to insolubility, interactions with calcium-dependent biologic processes, cytotoxic effects, and inhibition of mononuclear phagocytes (5). To minimize toxicity while maintaining desired paramagnetic properties in commercially available GBCM, gadolinium is chelated to organic ligands, conferring more favorable pharmacologic and toxicologic properties. Most GBCM distribute primarily in extracellular fluid, demonstrate little protein binding, and are predominantly excreted in urine by glomerular filtration. However, some GBCM exhibit more pronounced protein binding and/or partial hepatobiliary excretion.

GBCM are categorized as linear or macrocyclic based on the molecular structure of the organic ligand and as nonionic or ionic based on their net charge in solution (Table 1). In general, macrocyclic GBCM are thermodynamically very stable (ie, low ratio of free gadolinium to complexed ligand at equilibrium) and more kinetically inert (ie, longer half-life for dissociation of gadolinium from its ligand) than are linear GBCM (6).

NSF and GBCM Exposure

NSF is a potentially debilitating and sometimes fatal systemic fibrotic condition that occurs almost exclusively in patients with AKI or severe CKD (estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m²). Skin and subcutaneous abnormalities (eg, skin thickening, contractures, pruritus, hyperpigmenta-

tion) and ocular findings (scleral plaques) are common, but NSF also can cause fibrosis of the viscera (eg, lungs, esophagus, and heart). The diagnosis of NSF requires a combination of clinical history, clinical criteria using a specified scoring system, and deep skin biopsy (7).

The development of NSF is almost certainly triggered by exposure to GBCM, but the development of disease after exposure to GBCM is idiosyncratic, and the mechanism is still poorly understood (8,9). The interval between GBCM exposure and onset of symptoms attributed to NSF ranges from the same day to approximately 10 years (median, 42 days) (8).

Unconfounded NSF refers to cases where there is confirmation that only one specific GBCM was administered in single or multiple doses before the development of NSF. Confounded NSF refers to cases in which there was more than one specific GBCM administered prior to development of NSF, or there was no confirmation that only one specific GBCM was administered.

By 2012, 1603 NSF cases had been reported to the United States Food and Drug Administration Adverse Events Reporting System. This number may have included duplicates, confounded cases, and unconfirmed cases (9). Since 2008, the number of reported cases of NSF has dramatically declined to single digits, likely secondary to regulatory actions, decreased utilization of group I GBCM, and changes in clinical practice guidelines (8,10). It also is possible there is underreporting of NSF to the Food and Drug Administration (11).

Key Questions and ACR-NKF Statements

Table 2 summarizes the major ACR-NKF consensus statements on use of intravenous GBCM in patients with kidney disease, and Table 3 provides comparison of these statements to historical ACR (from 2018) and Kidney Disease Improving Global Outcomes (from 2013) guidelines.

Who Is at Risk for NSF?

The link between GBCM and NSF was first proposed in 2006 (12,13) and has since been confirmed in numerous studies (8). Patients at greatest risk for NSF include those undergoing renal replacement therapy, those with AKI, and those at stages 4 or 5 CKD with exposure to a group I GBCM (Table 1), especially if repeated doses of a group I GBCM are administered at higher-than-recommended doses (8). In a study of 83 121 patients, the incidence of NSF among 58 patients with AKI who received high-dose group I GBCM was 19% (14). In a 2011 systematic review (15) of 370 biopsy-confirmed cases of NSF, the incidence in individual series ranged 0%–18%, with 99% (228 of 231) of verified administrations being group I GBCM or a mixed GBCM exposure. All patients with known kidney function in that series ($n = 353$ of 370) were undergoing dialysis, had eGFR less than 30 mL/min per 1.73 m², or had AKI (15). The authors acknowledged controversy regarding the three cases linked to a macrocyclic agent (15). There are rare published reports of NSF in patients with stage 3 CKD (eGFR of 30–59 mL/min per 1.73 m²) (16–18). Some of these reports were of questionable validity, and there are no published reports of NSF in patients with eGFR greater than or equal to 60 mL/min per 1.73 m².

Table 1: ACR Classification of GBCM Relative to Association with NSF

U.S. Trade Name	Generic Name	Structure	ACR Group
Omniscan	Gadodiamide	Linear nonionic	I
OptiMark	Gadoversetamide	Linear nonionic	I
Magnevist	Gadopentetate dimeglumine	Linear ionic	I
MultiHance	Gadobenate dimeglumine	Linear ionic	II
ProHance	Gadoteridol	Macrocyclic nonionic	II
Gadavist	Gadobutrol	Macrocyclic nonionic	II
Dotarem	Gadoterate meglumine	Macrocyclic ionic	II
Clariscan	Gadoterate meglumine	Macrocyclic ionic	II
Eovist	Gadoxetate disodium	Linear ionic	III

Note.—Group I: gadolinium-based contrast media (GBCM) associated with the greatest number of nephrogenic systemic fibrosis (NSF) cases. Group I GBCM are no longer advertised in the United States. Group II: GBCM associated with few, if any, unconfounded cases of NSF. Group III: GBCM for which data remains limited regarding NSF risk, but for which few, if any, unconfounded cases of NSF have been reported. ACR = American College of Radiology.

Table 2: Summary of Major ACR-NKF Consensus Statements on Use of Intravenous Gadolinium-containing Contrast Media in Patients with Kidney Disease

Summary

1. Patients undergoing renal replacement therapy, patients with AKI, and patients with stage 4 or 5 CKD who are exposed to a group I GBCM—especially repeated doses of a higher off-label dose of a group I GBCM—are at greatest risk of NSF.
2. Risk of NSF differs between GBCM and can be stratified into three GBCM groups (group I: highest risk; group II: very low risk; group III: likely very low risk but insufficient confirmatory evidence).
3. The risk of NSF increases with larger doses of group I GBCM. The dose-related risk of NSF from group II and group III GBCM is unknown, but in general the lowest diagnostic dose of GBCM should be used.
4. Group II GBCM should not be withheld or delayed if harm would result from not proceeding with an indicated contrast-enhanced MRI.
5. Kidney function screening is optional for group II GBCM but is necessary for group III GBCM.
6. Direct communication between the radiologist and referring provider regarding risk of NSF is not necessary for group II GBCM administration, but it is suggested for group III GBCM administration in patients with eGFR <30 mL/min per 1.73 m² or AKI.
7. The risk of NSF is very low for a standard dose (0.1 mmol/kg) of group II GBCM, even in patients with eGFR <30 mL/min per 1.73 m² or AKI.
8. Prophylaxis is not indicated for the prevention of NSF. Risk mitigation strategies can include awaiting kidney function recovery and use of group II GBCM.
9. Dialysis should not be initiated or altered based on group II or group III GBCM administration.
10. On-label dosing of group II or group III GBCM does not have a clinically important risk of nephrotoxicity.
11. If multiple urgent group II or group III GBCM doses are indicated, subsequent dose(s) should not be delayed for fear of NSF. If not urgent, delaying the subsequent dose(s) >24 hours or performing intercurrent dialysis can promote GBCM clearance.
12. The above recommendations should not be altered in patients receiving nephrotoxic medications, chemotherapy, or contrast-enhanced CT.
13. The above recommendations also apply to pediatric patients. The risk of NSF in pediatric patients appears to be low, but data are limited. The Bedside Schwartz equation or the creatinine-cystatin C-based CKiD equation should be used to assess eGFR in infants and children.

Note.—ACR = American College of Radiology, AKI = acute kidney injury, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, GBCM = gadolinium-based contrast media, NKF = National Kidney Foundation, NSF = nephrogenic systemic fibrosis.

NSF does not appear to be related to the cause or duration of kidney disease (8). Initial concerns about other risk factors such as coincident liver disease without associated kidney disease have not been supported in the literature (19).

Is the Risk of NSF the Same for All GBCM?

The ACR categorizes GBCM into three groups (Table 1) based on their risk association with NSF (20). This risk classification is endorsed in these statements.

Group I: Nearly all unconfounded cases of NSF have been linked to one of the three linear group I GBCM. These GBCM are no longer advertised in the United States and have been withdrawn from the market in other countries. Therefore, no specific recommendations regarding group I GBCM use are included in this document.

Group II: Few, if any, unconfounded cases of NSF have been associated with group II GBCM. These include the linear ionic GBCM gadobenate dimeglumine (MultiHance; Bracco

Table 3: Comparison of Major Current ACR-NKF Consensus Statements to Historical ACR (from 2018) and KDIGO (from 2013) Guidelines

Consensus Statement	Comparison to Historical ACR and KDIGO Guidelines
1	ACR: Similar statement of risk KDIGO: Similar statement of risk, but macrocyclic versus linear GBCM are considered rather than ACR GBCM groups
2	ACR: Identical GBCM risk grouping KDIGO: GBCM risk is differentiated by macrocyclic versus linear structure. Gadobenate dimeglumine (linear ionic group II) and gadoxetate disodium (linear ionic group III) are not distinguished from linear group I GBCM.
3	ACR: Similar recommendation KDIGO: Closely spaced repeat doses of GBCM should be avoided.
4	ACR: Similar recommendation KDIGO: Similar recommendation
5	ACR: Similar recommendation KDIGO: Not specifically addressed, but screening for all GBCM is implied
6	ACR: Not specifically addressed KDIGO: Not specifically addressed
7	ACR: Similar recommendation KDIGO: Macrocyclic GBCM are recommended if eGFR <30 mL/min per 1.73 m ² and GBCM should be avoided if eGFR <15 mL/min per 1.73 m ² unless there is no alternative.
8	ACR: Use of prophylaxis is not specifically addressed. KDIGO: Use of prophylaxis is not specifically addressed.
9	ACR: For patients already undergoing dialysis, GBCM should be administered as soon as possible before dialysis. Repeated dialysis sessions are not recommended. KDIGO: For patients already undergoing dialysis, dialysis should be performed immediately after GBCM administration and possibly again 24 hours later.
10	ACR: Not specifically addressed KDIGO: Not specifically addressed
11	ACR: Group II GBCM should be used when multiple doses are indicated. KDIGO: Closely spaced doses should be avoided.
12	ACR: Not specifically addressed KDIGO: Not specifically addressed
13	ACR: Similar recommendation KDIGO: Measurement of eGFR is challenging in neonates and young infants. Use of GBCM in neonates should be avoided if possible due to difficulty assessing kidney function and immature kidneys.

Note.—See also Table 2. ACR = American College of Radiology, eGFR = estimated glomerular filtration rate, GBCM = gadolinium-based contrast media, KDIGO = Kidney Disease Improving Global Outcomes, NKF = National Kidney Foundation. Source.—References 10, 46–49.

Diagnostics, Princeton, NJ; ~5% hepatobiliary excretion) and all macrocyclic GBCM (gadoterate meglumine [Dotarem; Guerbet, Villepinte, France and Clariscan; GE Healthcare, Oslo, Norway], gadobutrol [Gadavist; Bayer Healthcare, Whippany, NJ], and gadoteridol [ProHance; Bracco Diagnostics]). Gadobenate dimeglumine (MultiHance; Bracco Diagnostics) is considered group II because the evidence supporting a very low risk of NSF is actually greater for gadobenate than it is for the macrocyclic GBCM (21–23). The mechanism is unclear, but it may relate to its partial hepatobiliary excretion. In a review of 405 patients diagnosed with NSF (8), group II GBCM exposures were reported in 23 patients; however, only two were unconfounded (16,21). Two additional patients with NSF were administered a group II GBCM with another unknown GBCM, precluding an assessment of confounding (22). In a 2019 systematic review and meta-analysis (23) of 4931 group II GBCM administrations in patients with stage 4 or 5 CKD (eGFR <30 mL/min per 1.73 m²), the risk of NSF was 0% (zero cases in 4931 subjects; upper bound of the 95% confidence interval: 0.07%). A subsequent subanalysis

of these data stratified by CKD stage found the upper bound of the 95% confidence interval of risk to be 0.2% (one case for every 500 exposed patients) for stage 5D CKD (eGFR <15 mL/min per 1.73 m² undergoing maintenance dialysis) based on zero cases in 1849 exposed individuals, and 0.5% (one case for every 200 exposed patients) for stage 5 CKD (eGFR <15 mL/min per 1.73 m² not undergoing maintenance dialysis) based on zero cases in 732 exposed individuals (24). For all patients with stage 5 or 5D CKD, the upper bound of the 95% confidence interval of risk was 0.1% (one case for every 1000 exposed patients) based on zero cases in 2581 exposed individuals (24). Thus, while the risk of NSF following exposure to group II GBCM is low, that risk estimate is based on data from only 2581 individuals with CKD stages 5 ($n = 732$) or 5D ($n = 1849$) (24).

Group III: Few, if any, unconfounded cases of NSF have been associated with group III GBCM administration, but data remain limited about NSF risk due to few published administrations in high-risk patients. The only currently available group III GBCM is gadoxetate disodium (Eovist or Primovist; Bayer

Healthcare; ~50% hepatobiliary excretion). It is marketed and primarily used for the detection and characterization of focal liver lesions. No unconfounded cases of NSF have been reported for gadoxetate disodium. The largest published study of NSF risk from gadoxetate disodium included one cohort of 85 patients with stage 4 or 5 CKD or undergoing dialysis, and another cohort of 193 patients with stage 3 CKD; no NSF events were observed (25).

The difference in NSF risk among GBCM groups is likely explained by the different kinetic liabilities of linear (more labile) and macrocyclic (less labile) GBCM, and differences in pharmacologic properties among GBCM (ie, degree of hepatobiliary excretion and/or degree of protein binding) (26). A combination of other factors, including market share, number of years a GBCM was in use, differential dosing, differences in patient populations, reporting bias, and confounded NSF events may have contributed to differences in apparent risk. To address the possibility of market share bias as a potential explanation for apparent risk differences, a hypothetical balanced market share analysis was performed in conjunction with a systematic review of biopsy-confirmed NSF (8). That analysis determined that group I GBCM were associated with an approximately 190-fold increased rate of NSF compared with group II GBCM (1.52 vs 0.008 per million average-risk population exposures; $P < .001$) (8).

Is There an Association between NSF and the Dose of GBCM?

Before the association of GBCM with NSF, contrast media-enhanced MRI and MR angiography examinations with intravenous group I GBCM were commonly substituted for iodinated contrast-enhanced CT or CT angiography in patients with impaired kidney function. In the United States, it was previously common to administer “double” or greater doses of group I GBCM because GBCM were considered nonnephrotoxic. Also, high doses of GBCM were occasionally administered intra-arterially for standard angiography and intravenously for CT scans in lieu of iodinated contrast media in patients with impaired kidney function. These now-abandoned (except in some instances of cardiac MRI) clinical practices likely increased the risk of NSF.

In a review of 182 patients with NSF, only 19 (10%) patients received the standard dose (0.1 mmol/kg) of GBCM, while 163 (90%) received more than the standard dose (27). In a retrospective cohort study, NSF was documented in zero of 74 124 (0%) patients who received the standard dose (approximately 0.1 mmol/kg) of GBCM and 15 of 8997 (0.17%; $P < .001$) patients who received a higher dose (20–60 mL, approximately 0.2–0.4 mmol/kg) (14). All confirmed NSF associations occurred after administration of a group I GBCM. In a study of 849 patients undergoing maintenance dialysis (28), multiple presumably group I GBCM exposures increased the risk of developing NSF compared with a single exposure or no exposure (odds ratio, 44.5 for multiple exposures vs 6.7 for single exposure; and 0.0 for no exposures). These data demonstrate increased risk for NSF after administration of larger doses of group I GBCM.

Although the risk of NSF following intravenous administration of Food and Drug Administration–approved doses of group

II and possibly group III GBCM is extremely low, the risk associated with greater doses or intra-arterial administration has not been assessed. Therefore, the risk-to-benefit ratio determination for these applications is less certain and subject to radiologist consideration. In general, the lowest diagnostic dose of GBCM should be used, regardless of whether it is on-label or off-label.

Should Screening for Kidney Disease Be Used to Identify Patients at Risk for NSF prior to GBCM Administration?

In 2010, the Food and Drug Administration issued a black box warning for all GBCM with the recommendation of kidney function screening before GBCM administration to identify patients with AKI or stage 4 or 5 CKD (29). However, it is now apparent that the risk of NSF varies by GBCM and is extremely low for group II GBCM, even in high-risk patients (3,7,8,29). Based on these updated data, the ACR, European Society of Urogenital Radiology, and Canadian Association of Radiology have issued recommendations liberalizing the administration of group II GBCM in high-risk patients (20,30,31). In contrast to the Food and Drug Administration, these organizations do not consider group II GBCM to be contraindicated in high-risk patients and consider kidney function screening prior to use of group II GBCM optional. However, unlike the ACR and the Canadian Association of Radiology, the European Society of Urogenital Radiology advises “caution” when administering group II GBCM to patients with eGFR less than 30 mL/min per 1.73 m² (30).

Although there are no validated unconfounded cases of NSF associated with group III GBCM, the available data are sparse as utilization has been much less than group I and group II GBCM. Thus, screening for kidney disease is still recommended when a group III GBCM is used.

If Kidney Function Screening Is Indicated, How Should Screening for Kidney Disease Be Performed and which Patient Risk Factors Should Be Used to Trigger Kidney Function Assessment?

Screening for kidney disease prior to GBCM administration is a two-step process. First, if kidney function screening is indicated, clinical risk factors are evaluated that predict whether AKI or stage 4 or 5 CKD might be present. Second, if one or more clinical risk factors is present, eGFR measurement is obtained. If a patient has active AKI or is undergoing dialysis, kidney function screening is not indicated because eGFR measurement is not reliable in those settings, and these patients are already at high risk for NSF. Details of kidney function screening including methods and risk factors are provided in a previously published ACR-NKF consensus document on intravenous iodinated contrast media (4).

What eGFR Threshold, If Any, Should Be Used by Radiology Practices to Trigger Direct Contact with the Referring Provider prior to Administering GBCM, and Should It Be Modified by Other Risk Factors?

Depending on individual practice patterns, group II GBCM may be administered to high-risk patients without kidney

function screening and without contact with the referring provider. If a patient scheduled to receive group III GBCM is determined to be at high risk for NSF (ie, AKI or eGFR <30 mL/min per 1.73 m²), this should prompt active consideration of the risks and benefits associated with GBCM-enhanced imaging, consideration of alternative diagnostic strategies, and communication between the radiologist and the referring provider. Although written documentation of informed consent is not required before administration of group II or group III GBCM, patients with known AKI or known stage 4 or 5 CKD should be informed of the potential risk of NSF associated with GBCM administration, the reason GBCM administration is indicated, and whether there are viable alternative diagnostic strategies.

In a Patient with Kidney Disease, Is There Prophylaxis Available that Can Reduce the Risk of NSF?

No prophylaxis is known to reduce the risk of NSF in high-risk patients. Risk mitigation strategies include awaiting kidney function recovery prior to GBCM administration and using group II GBCM.

Should Dialysis Be Initiated or Accelerated in Patients with Kidney Disease Who Receive GBCM?

Although hemodialysis is effective in removing GBCM from the body (32–34), a reduction in risk of NSF is only theoretical and has not been demonstrated in randomized controlled trials. Hemodialysis is more effective than peritoneal dialysis in removing GBCM (34). When medically appropriate, GBCM administration optimally should be timed before a regularly scheduled hemodialysis session in patients who are already undergoing dialysis. If this is not feasible, dialysis should be conducted at its regularly scheduled day and time. No form of dialysis is considered prophylactic for NSF (34).

Even though dialysis can improve GBCM clearance, due to the attendant risk of catheter placement and infection, the possibility of worsening kidney function in those with AKI and CKD, and the perceived very low risk of NSF from group II and group III GBCM, dialysis should not be initiated or altered based on group II or group III GBCM administration. Specifically, daily dialysis or multiple per-day dialysis sessions are not considered necessary.

Should GBCM Be Considered Nephrotoxic When Administered Using an On-Label Dose?

Although GBCM are colloquially assumed to be nonnephrotoxic, data indicate they may be nephrotoxic in humans and animals at sufficiently high doses (35–38). AKI is listed as an adverse reaction in the prescribing information for all GBCM in the United States. However, prior reports of nephrotoxicity in humans are likely related to very high off-label dosing of GBCM (37,39), which is no longer applicable in the context of current clinical care. There are no well-controlled clinical studies demonstrating a clinically important nephrotoxic risk at on-label doses of GBCM (40,41). Existing literature imply-

ing a potential risk of nephrotoxicity in humans are uncontrolled retrospective studies and case reports (42–44). Since on-label dosing of intravenous GBCM is not associated with a clinically relevant risk of AKI, no prophylaxis is indicated for patients who will receive an on-label dose of group II or group III GBCM.

Should Any of the Above Recommendations Be Altered in Patients Receiving Nephrotoxic Medications, Chemotherapy, or Contrast-enhanced CT?

In general, the above recommendations should not be altered in patients receiving nephrotoxic medications, chemotherapy, or contrast-enhanced CT. Nephrotoxic drugs do not need to be withheld prior to an on-label dose of group II or group III GBCM. Contrast-enhanced MRI may be performed immediately before or after contrast-enhanced CT (and vice versa) without additional safety concerns. Because of the weak x-ray attenuating properties of GBCM, residual interstitial, urinary tract, or vascular GBCM may mildly alter the appearance of normal and pathologic structures at CT. However, for almost all clinical indications, residual in vivo GBCM will not affect the diagnostic value of CT.

How Much Time Should Elnapse between Sequential GBCM Administrations?

Similar to the risk in patients receiving a single standard dose (0.1 mmol/kg) of group II or group III GBCM, the risk of NSF from multiple, closely spaced, standard doses of group II or group III GBCM in patients with eGFR greater than or equal to 30 mL/min per 1.73 m² is likely very small. The risk of multiple closely spaced doses has not been evaluated in patients with eGFR less than 30 mL/min per 1.73 m². If there is an urgent indication that requires closely spaced doses, the examination(s) should not be delayed for fear of NSF. If it is not medically inappropriate to delay a subsequent examination, permitting greater than 24 hours to elapse or an intercurrent dialysis session may allow greater clearance of GBCM.

Should Any of the Above Be Altered in the Pediatric Population?

In general, the aforementioned recommendations, including those for the group III GBCM gadoxetate disodium, should not be altered for infants and children. Kidney function measurement in infants and children should be evaluated by the Bedside Schwartz equation or creatinine-cystatin C-based CKiD equation rather than by eGFR equations that were developed and validated in adults (45,46). NSF has been reported rarely in children (23 unique children aged 6 years or older from 1997–2012) (47). Of the 17 children with NSF and reported exposure to GBCM, most received only group I GBCM. None received a group III GBCM, and there are no unconfounded cases in pediatric patients from a group II GBCM (47). The risk of NSF in pediatric patients exposed to group II or group III GBCM is unknown. Interestingly, there have been no reported cases of NSF in neonates or infants

despite immature kidney function and eGFR measurements commonly less than 30 mL/min per 1.73 m².

Summary

These joint consensus statements by the American College of Radiology and the National Kidney Foundation are intended to improve and standardize the care of patients with impaired kidney function who have indication(s) to receive intravenous gadolinium-based contrast media (GBCM). The risk of nephrogenic systemic fibrosis (NSF) or nephrotoxicity following administration of a standard dose (0.1 mmol/kg) of a group II GBCM is extremely low. The risk estimate of NSF for group II GBCM in patients with stage 5 or 5D chronic kidney disease is based on data from 2581 individuals. It is possible that NSF may rarely occur in this population. The harms of delaying or withholding group II GBCM for a clinically indicated MRI in a patient with acute kidney injury or estimated glomerular filtration rate less than 30 mL/min per 1.73 m² may outweigh the risk of NSF, regardless of dialysis status. The safety margin of group II GBCM should be considered with the potential harm of delayed diagnosis or misdiagnosis. Further study investigating the clinical benefits of GBCM for common indications can improve risk-benefit decision making. Kidney function screening prior to group II GBCM administration is optional. It is not necessary to initiate or alter an established dialysis schedule based on group II or group III GBCM administration. These recommendations also apply to patients receiving nephrotoxic medications, chemotherapy, or contrast-enhanced CT.

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

Disclosures of Conflicts of Interest: J.C.W. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for Bracco and GE Healthcare; has grants/grants pending with Ascella Pharma. Other relationships: is a medicolegal consultant for Bayer Healthcare. R.A.R. disclosed no relevant relationships. J.Y. disclosed no relevant relationships. C.L.W. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: has grants/grants pending with GE Healthcare. Other relationships: disclosed no relevant relationships. D.F. disclosed no relevant relationships. R.J.M. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for GE Healthcare; has grants/grants pending with Bayer and GE Healthcare. Other relationships: disclosed no relevant relationships. M.A.P. disclosed no relevant relationships. J.R.D. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: has grants/grants pending with Bracco Diagnostics and Guerbet. Other relationships: disclosed no relevant relationships. M.S.D. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: receives royalties from Wolters Kluwer. Other relationships: disclosed no relevant relationships.

References

- Balzer T. Presence of gadolinium (Gd) in the brain and body. Presentation to the Medical Imaging Drugs Advisory Committee, FDA. Silver Spring, Md: U.S. Food and Drug Administration, 2017.
- McDonald RJ, Levine D, Weinreb J, et al. Gadolinium retention: a research roadmap from the 2018 NIH/ACR/RSNA workshop on gadolinium chelates. *Radiology* 2018;289(2):517–534.
- Maripuri A, Jahansen KL. Risk of Gadolinium-Based Contrast Agents in Chronic Kidney Disease—Is Zero Good Enough? *JAMA Intern Med* 2020;180(2):230–232. <https://doi.org/10.1001/jamainternmed.2019.5278>.
- Davenport MS, Perazella MA, Yee J, et al. Use of Intravenous Iodinated Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. *Radiology* 2020;294(3):660–668.
- Rogosnitzky M, Branch S. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. *Biometals* 2016;29(3):365–376.
- Idée JM, Port M, Robic C, Medina C, Sabatou M, Corot C. Role of thermodynamic and kinetic parameters in gadolinium chelate stability. *J Magn Reson Imaging* 2009;30(6):1249–1258.
- Girardi M, Kay J, Elston DM, Leboit PE, Abu-Alfa A, Cowper SE. Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. *J Am Acad Dermatol* 2011;65(6):1095–1106.e7.
- Attari H, Cao Y, Elmholt TR, Zhao Y, Prince MR. A systematic review of 639 patients with biopsy-confirmed nephrogenic systemic fibrosis. *Radiology* 2019;292(2):376–386.
- Bennett CL, Qureshi ZP, Sartor AO, et al. Gadolinium-induced nephrogenic systemic fibrosis: the rise and fall of an iatrogenic disease. *Clin Kidney J* 2012;5(1):82–88.
- Davenport MS. Virtual Elimination of Nephrogenic Systemic Fibrosis: A Medical Success Story with a Small Asterisk. *Radiology* 2019;292(2):387–389.
- Alatawi YM, Hansen RA. Empirical estimation of under-reporting in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). *Expert Opin Drug Saf* 2017;16(7):761–767.
- Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006;21(4):1104–1108.
- Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006;17(9):2359–2362.
- Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. *Radiology* 2008;248(3):807–816.
- Zou Z, Zhang HL, Roditi GH, Leiner T, Kucharczyk W, Prince MR. Nephrogenic systemic fibrosis: review of 370 biopsy-confirmed cases. *JACC Cardiovasc Imaging* 2011;4(11):1206–1216.
- Lohani S, Golenbiewski J, Swami A, Halalau A. A unique case of nephrogenic systemic fibrosis from gadolinium exposure in a patient with normal eGFR. *BMJ Case Rep* 2017;2017:bcr-2017-221016.
- Shibui K, Kataoka H, Sato N, Watanabe Y, Kohara M, Mochizuki T. A case of NSF attributable to contrast MRI repeated in a patient with Stage 3 CKD at a renal function of eGFR > 30 mL/min/1.73 m². *Jpn J Nephrol* 2009;51:676.
- Swaminathan S, Shah SV. New insights into nephrogenic systemic fibrosis. *J Am Soc Nephrol* 2007;18(10):2636–2643.
- Smorodinsky E, Ansdell DS, Foster ZW, et al. Risk of nephrogenic systemic fibrosis is low in patients with chronic liver disease exposed to gadolinium-based contrast agents. *J Magn Reson Imaging* 2015;41(5):1259–1267.
- American College of Radiology. Manual on contrast media. Version 10.3. Reston, Va: American College of Radiology, 2018. <https://www.acr.org/Clinical-Resources/Contrast-Manual>. Accessed December 21, 2019.
- Elmholt TR, Jørgensen B, Ramsing M, Pedersen M, Olesen AB. Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gadobutrol. *NDT Plus* 2010;3(3):285–287.
- Elmholt TR, Olesen AB, Jørgensen B, et al. Nephrogenic systemic fibrosis in Denmark—a nationwide investigation. *PLoS One* 2013;8(12):e82037.
- Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. 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. *JAMA Intern Med* 2020;180(2):223–230.
- Shankar PR, Davenport MS. Risk of nephrogenic systemic fibrosis in stage 4 and 5 chronic kidney disease following group II gadolinium-based contrast agent administration: subanalysis by chronic kidney disease stage. *Radiology* 2020. 10.1148/radiol.2020201492. Published online August 18, 2020.
- Lauenstein T, Ramirez-Garrido F, Kim YH, et al. Nephrogenic systemic fibrosis risk after liver magnetic resonance imaging with gadoxetate disodium in patients with moderate to severe renal impairment: results of a prospective, open-label, multicenter study. *Invest Radiol* 2015;50(6):416–422.
- Tweedle M, Kanal E, Muller R. Considerations in the selection of a new gadolinium-based contrast agent. *Appl Radiol* 2014;(Suppl):1–11. <https://www.appliedradiology.com/articles/considerations-in-the-selection-of-a-new-gadolinium-based-contrast-agent>.
- Prince MR, Zhang HL, Roditi GH, Leiner T, Kucharczyk W. Risk factors for NSF: a literature review. *J Magn Reson Imaging* 2009;30(6):1298–1308.

28. Othersen JB, Maize JC, Woolson RF, Budisavljevic MN. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. *Nephrol Dial Transplant* 2007;22(11):3179–3185.
29. FDA Drug Safety Communication. New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warnings-using-gadolinium-based-contrast-agents-patients-kidney>. Accessed January 7, 2020.
30. ESUR Guidelines on Contrast Agents. Version 10.0. http://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_10.0_Final_Version.pdf. Published March 2018. Accessed December 22, 2019.
31. Schieda N, Maralani PJ, Hurrell C, Tsampalieros AK, Hiremath S. Updated clinical practice guideline on use of gadolinium-based contrast agents in kidney disease issued by the Canadian Association of Radiologists. *Can Assoc Radiol J* 2019;70(3):226–232.
32. Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acad Radiol* 1998;5(7):491–502.
33. Okada S, Katagiri K, Kumazaki T, Yokoyama H. Safety of gadolinium contrast agent in hemodialysis patients. *Acta Radiol* 2001;42(3):339–341.
34. Yee J. Prophylactic hemodialysis for protection against gadolinium-induced nephrogenic systemic fibrosis: A Doll's House. *Adv Chronic Kidney Dis* 2017;24(3):133–135.
35. Sam AD 2nd, Morasch MD, Collins J, Song G, Chen R, Pereles FS. Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. *J Vasc Surg* 2003;38(2):313–318.
36. Ergün I, Keven K, Uruç I, et al. The safety of gadolinium in patients with stage 3 and 4 renal failure. *Nephrol Dial Transplant* 2006;21(3):697–700.
37. Heinrich MC, Kuhlmann MK, Kohlbacher S, et al. Cytotoxicity of iodinated and gadolinium-based contrast agents in renal tubular cells at angiographic concentrations: in vitro study. *Radiology* 2007;242(2):425–434.
38. McDonald RJ, McDonald JS, Dai D, et al. Comparison of Gadolinium Concentrations within Multiple Rat Organs after Intravenous Administration of Linear versus Macrocytic Gadolinium Chelates. *Radiology* 2017;285(2):536–545.
39. Celiker FB, Tumkaya L, Mercantepe T, et al. Effects of gadodiamide and gadoteric acid on rat kidneys: a comparative study. *J Magn Reson Imaging* 2019;49(2):382–389.
40. Gemery J, Idelson B, Reid S, et al. Acute renal failure after arteriography with a gadolinium-based contrast agent. *AJR Am J Roentgenol* 1998;171(5):1277–1278.
41. Boyden TF, Gurm HS. Does gadolinium-based angiography protect against contrast-induced nephropathy?: a systematic review of the literature. *Catheter Cardiovasc Interv* 2008;71(5):687–693.
42. Naito S, Tazaki H, Okamoto T, et al. Comparison of nephrotoxicity between two gadolinium-contrasts, gadodiamide and gadopentetate in patients with mildly diminished renal failure. *J Toxicol Sci* 2017;42(3):379–384.
43. Akgun H, Gonlusen G, Cartwright J Jr, Suki WN, Truong LD. Are gadolinium-based contrast media nephrotoxic? A renal biopsy study. *Arch Pathol Lab Med* 2006;130(9):1354–1357.
44. Takahashi EA, Kallmes DF, Mara KC, Harmsen WS, Misra S. Nephrotoxicity of gadolinium-based contrast in the setting of renal artery intervention: retrospective analysis with 10-year follow-up. *Diagn Interv Radiol* 2018;24(6):378–384.
45. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20(3):629–637.
46. Staples A, LeBlond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. *Pediatr Nephrol* 2010;25(11):2321–2326.
47. Nardone B, Saddleton E, Laumann AE, et al. Pediatric nephrogenic systemic fibrosis is rarely reported: a RADAR report. *Pediatr Radiol* 2014;44(2):173–180.