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STATE OF PRACTICE

# ASNR Statement on Gadolinium-Based Contrast Agent Use in Patients with Chronic Kidney Disease

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## ABSTRACT

**BACKGROUND:** Beginning in 2006, neuroradiologists became increasingly aware of the risk of nephrogenic system fibrosis (NSF) when patients suffering from chronic kidney disease (CKD) received gadolinium-based contrast agents (GBCAs) in conjunction with MRI scans. Radiology practices began withholding GBCAs from MRI patients with substantial CKD and instated a variety of safety measures to ensure that these individuals did not inadvertently receive GBCAs. As a result, the worldwide incidence of NSF was dramatically reduced. Since that time, a wealth of research on NSF and its etiology has found few unconfounded cases associated with those GBCAs categorized as Group II agents by the American College of Radiology.

**METHODS:** In 2023 and 2024, members of the American Society of Neuroradiology (ASNR) Standards and Guidelines Committee reviewed new research evidence on GBCA safety and its relevance to current MRI contrast administration guidelines for patients with CKD. This focused on systematic reviews and meta-analyses conducted during the past five years. Upon consideration of this literature, recommendations for administration of GBCAs to patients with CKD were formulated.

**KEY MESSAGE:** For neuroimaging applications, the ASNR recommends that Group II GBCAs no longer be withheld in patients with CKD when these agents are medically indicated for diagnosis. Moreover, if Group II GBCAs are exclusively used in an MRI practice, other safety measures such as checking renal function or querying patients about chronic kidney disease can be discontinued.

**ABBREVIATIONS:** ACR = American College of Radiology; ASNR = American Society of Neuroradiology; CKD = chronic kidney disease; GBCA = gadolinium-based contrast agent; NSF = nephrogenic systemic fibrosis.

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## INTRODUCTION

The use of intravenous gadolinium-based contrast agents (GBCAs) is an important means of increasing diagnostic sensitivity and specificity in a wide variety of neurologic MRI applications[1]. Moreover, the administration of a GBCA bolus forms the basis for a variety of neurovascular examinations such as dynamic susceptibility contrast perfusion imaging and gadolinium bolus MRA. Since their inception, GBCAs have demonstrated a favorable safety profile with very few adverse outcomes despite millions of gadolinium doses administered since the introduction of the first agent, gadopentetate dimeglumine (Magnevist) in 1988[2]. Nevertheless, in 2006 case reports and epidemiologic studies began to implicate GBCA administration as a causative factor in the development of nephrogenic systemic fibrosis (NSF) in patients with compromised renal function[3]. Given the serious and chronic nature of NSF with reported mortality rates of up to 31%, various measures were undertaken by radiology practices across the world as a means of preventing new cases of NSF[4]. These included questioning patients receiving GBCAs about any history of renal disease, acquiring laboratory measures of renal function such as estimated glomerular filtration rate (eGFR), and withholding GBCAs in those patients exhibiting historical or laboratory evidence of Class IV or V chronic kidney disease (CKD) or acute kidney injury[5, 6].

Eventually, a mechanistic model of NSF emerged. GBCAs consist of elemental gadolinium bound within a chelate molecule that allows for its circulation and excretion[7]. In patients with renal compromise, impaired urinary excretion leads to prolonged gadolinium circulation time within the blood. Over time, the chelate molecules can become unstable releasing free gadolinium to deposit within a variety of bodily tissues[8]. In rare circumstances, the deposition of unchelated gadolinium leads to NSF[9]. It soon became clear that differing levels of chelate instability made some GBCAs more prone than others to cause NSF[7, 10]. In general, GBCAs with a linear chelate demonstrated more propensity to cause NSF in patients with CKD due to the fact that their molecular structures bind elemental gadolinium less tightly than GBCAs with a macrocyclic chelate[7].




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## ACR GBCA CATEGORIZATON

The varying risk for NSF among GBCAs prompted the American College of Radiology to categorize GBCAs into three groups as outlined in Table 1[11]. Group I GBCAs include the linear molecular agents gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), and gadoversetamide (Optimark). These Group I GBCAs carry the highest risk of NSF for renal compromised patients and are expressly contraindicated by the U.S. Food and Drug Administration for use in patients with an eGFR of less than 30 mL/min / 1.73 $m^2$ [12]. On the other hand, Group II GBCAs, which include all the macrocyclic GBCAs as well as the linear GBCAs gadobenate dimeglumine (Multihance) and gadoxetate disodium (Eovist / Primovist) are associated with very few unconfounded cases of NSF[13, 14]. In specific, there have been only 9 published case reports of unconfounded cases of NSF associated with Group II GBCAs[15].

ACR Group III is reserved for GBCAs for "which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported[11]." At the present time, there are no GBCAs assigned to Group III. The agent gadoxetate disodium was reclassified from Group III to Group II in April 2024[11]. While there are no unconfounded cases of NSF resulting from gadoxetate disodium, data regarding the use of this agent in patients with stage IV or V CKD is limited. Only 106 cases of gadoxetate disodium administration to patients with stage IV or V CKD have been reported in the literature and none of these developed NSF [16]. Of note, there are currently no neurologic applications for gadoxetate disodium. This GBCA is most often used for MR hepatobiliary imaging[17]. Consequently, gadoxetate disodium is outside the scope of this statement.

It is important to understand that the risk stratification in the ACR defined GBCA groups applies to patients with CKD and is not applicable to those with acute kidney injury. Although rare cases of NSF have been reported in patients with acute kidney injury, there is currently very little data available on the NSF risk associated with the various GBCAs in these patients[18].

## DECLINING NSF INCIDENCE

Once radiologists began withholding Group I GBCAs from patients with renal disease as stipulated by various regulatory agencies including the United States Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency, the worldwide incidence of NSF dramatically dropped[19-21]. Moreover, ever increasing amounts of research data have confirmed the safety of Group II GBCAs which demonstrate little risk for NSF even in patients with advanced CKD. Most of this research was subjected to a meta-analysis that was published by Woolen and colleagues in 2020[22]. In this well conducted meta-analysis that was comprised of 16 unique studies with 4931 patients, the risk of NSF in patients with stage IV or V CKD was found to be <0.07%, if the risk even exists. Given that the benefit of GBCA administration likely outweighs the miniscule risk of acquiring NSF from a Group II agent, there is growing consensus among both radiologists and nephrologists that withholding medically indicated Group II GBCAs in patients with Stage IV or V CKD is unnecessary[23]. The most recent ACR Manual on Contrast Media states "the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration"[11].

## ASNR RECOMMENDATIONS

In this context, a subcommittee appointed by the American Society of Neuroradiology Standards and Guidelines Committee reviewed recent high-level evidence regarding the risk of NSF after administration of GBCAs in patients with CKD. The search terms "nephrogenic systemic fibrosis", "gadolinium", as well as "systemic review" or "meta-analysis" were employed in a PubMed search for manuscripts published during the past five years (2019 to 2024). Eight publications met this search criteria. Three publications that focused on the treatment of NSF, intra-arterial administration of gadolinium, and solely on the GBCA gadoxetate disodium were excluded as not being pertinent to the issue under consideration[16, 24, 25]. After these exclusions, there were four remaining systematic reviews as well as the previously cited meta-analysis by Wollen and colleagues[13, 15, 18, 22, 26]. After considering this literature, the Standards and Guidelines Committee on behalf of the American Society of Neuroradiology provides the following recommendations:

1. As mandated by the FDA, Group I GBCAs should never be given to patients with a history of CKD.
2. In neuroimaging applications, Group II GBCAs should not be withheld from patients with CKD over concern for NSF.
3. If there is a valid clinical indication for GBCA administration, Group II GBCAs can be administered to patients with stage IV or V CKD without obtaining informed consent. As with all patients, GBCAs should only be administered when considered necessary by the supervising radiologist and should be given at the lowest dose needed for diagnosis.
4. If only Group II GBCAs are employed in a clinical practice, routinely questioning MRI patients about their history of renal disease or obtaining laboratory measures of renal function is unnecessary.
5. Recently, a newly approved high relaxivity GBCA was added to Group II: gadopiclenol (Elucirem / Vueway)[27]. This agent is expected to have a favorable safety profile because of its macrocyclic chelate. While gadopiclenol is probably safe in patients with CKD, this needs to be confirmed as the experience with this new contrast agent increases. Furthermore, this unknown risk needs to be assessed in the perspective that gadopiclenol allows the same or higher image enhancement while administering only half the amount of gadolinium atoms compared to other contrast agents, which may have some advantages in terms of potential gadolinium retention, especially in patients who will receive multiple doses of gadolinium contrast agent over the course of time[28, 29].
6. Although very few cases of NSF have been reported in the pediatric population as compared to adults with CKD, the above recommendations are applicable to pediatric patients with CKD[30]. As always, caution should be exercised in the administration of GBCAs to neonates and infants where the possibility of renal immaturity exists.

## CONCLUSION

In summary, scientific research over the last decade has established the safety of Group II GBCAs for use in patients with CKD. As long as Group II GBCAs are employed, the risk of NSF as the result of a gadolinium enhanced MRI scan is miniscule, if it even exists. Neuroradiologists should not withhold Group II GBCAs in patients with CKD when contrast enhanced MRI is clinically indicated for diagnosis. The potential benefit of a gadolinium enhanced MRI scan greatly outweighs any risk of NSF when appropriate GBCAs are employed.

**Table 1: Gadolinium-Based Contrast Agents by ACR Groups[11].**

| ACR Group | Generic Name | Product Name(s) | Chemical Structure | 3T Relaxivity |
|---|---|---|---|---|
| I | Gadopentetate Dimeglumine | Magnevist (Bayer Healthcare) | Linear / Ionic | 3.7 |
| I | Gadodiamide | Omniscan (GE Healthcare) | Linear / Non-ionic | 4 |
| I | Gadoversetamide | Optimark (Guerbet) | Linear / Non-ionic | 4.5 |
| II | Gadobenate Dimeglumine | Multihance (Bracco) | Linear / Ionic | 5.5 |
| II | Gadoterate Meglumine | Clariscan (GE Healthcare)<br>Dotarem (Guerbet) | Macrocyclic / Ionic | 3.5 |
| II | Gadobutrol | Gadavist (Bayer Healthcare)<br>Gadovost (Bayer Healthcare) | Macrocyclic / Non-ionic | 5 |
| II | Gadoteridol | Prohance (Bracco) | Macrocyclic / Non-ionic | 3.7 |
| II | Gadopiclenol | Elucirem (Guerbet)<br>Vueway (Bracco) | Macrocyclic / Non-ionic | 11.6 |
| II | Gadoxetate Disodium | Eovist (Bayer Healthcare)<br>Primovist (Bayer Healthcare) | Linear / Ionic | 6.2 |


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