

# Use of Gadolinium-Based Contrast Agents in Patients with Severe Renal Impairment. Absence of Risk Versus Caution: A Nephrologist's Perspective

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Nephrogenic systemic fibrosis (NSF) was initially reported in 2000 and was causally linked to gadolinium-based contrast agents (GBCAs) in 2006 (1,2). NSF with rare exceptions is limited to patients with severe CKD, with the vast majority on dialysis. The causal role of GBCAs has been confirmed in subsequent clinical and experimental studies, which led to restrictive policies about GBCA use in patients with severe CKD. As a result of these policies, reports of NSF have virtually disappeared. More recent clinical studies investigating the risk of NSF in severe CKD after exposure to GBCAs that bind gadolinium ( $Gd^{+3}$ ) more tightly to the chelate have not demonstrated a risk of NSF (3). These observations have resulted in recommendations by some organizations such as the American College of Radiology (ACR) that state that GBCAs with high  $Gd^{+3}$ -binding properties (termed group 2 GBCAs, Table 1) can be safely used without risk of NSF in patients with severe CKD (4). The ACR states that because the risk of NSF with group 2 GBCAs is very low or nonexistent, these GBCAs can be safely given to patients with severe CKD without informed consent, and assessment of renal function by laboratory testing or questionnaire pre-GBCA is optional. The ACR qualifies this recommendation by stating that GBCAs should be administered only when deemed necessary using the lowest dose needed for diagnosis, that the risk of administering a group 2 GBCA in a high-risk patient must be balanced against the risk of not performing a needed contrast-enhanced study, and in patients with no residual renal function it is reasonable to use a contrast-enhanced computed tomography study if the anticipated diagnostic yield is similar. The recommendations of the ACR and other professional societies with similar recommendations are opposite to the restrictive policies of GBCA use, which have been in place since 2006 and have resulted in a current controversy about the safety of GBCA use in high-risk patients.

Two recent publications in *Kidney360* on this subject exemplify this controversy. In an editorial, Soloff and Wang (5) discuss the key issues past and present in the use of GBCAs in patients with severe CKD, and present the radiologist's perspective on this topic. The

authors conclude that *current data support the safe use of the group 2 agents at recommended doses in patients with AKI, CKD stage 4 or 5, or on dialysis. Although the safety of these agents may be questioned in animal studies, the benefit of using these agents in making accurate and important clinical diagnoses has far outweighed the small theoretical risk of developing NSF.*

The opposite view is expressed in an article by Do *et al.* (6), in which the physiochemical properties of the various GBCAs and their roles in NSF, brain deposition, and nephrotoxicity are reviewed. Do *et al.* note that the studies demonstrating an absence of NSF with group 2 GBCA exposure in high-risk patients are limited by their retrospective nature, lack of statistical power, limited dose exposure, and reliance on equations of eGFR, which have inherent accuracy limitations. The authors conclude that the current use of GBCAs are *not without risk and their long-term biologic and clinical effects remain to be seen.* They further conclude that *there is no renal function at which GBCA use is absolutely safe and risk free.*

How should nephrologists and other physicians view these two opposite positions? Almost all of the reports of NSF have occurred with the linear GBCAs gadodiamide, gadopentetate dimeglumine, and gadoversetamide, which bind the toxic  $Gd^{+3}$  to a chelate less strongly than other available GBCAs. After initial observations of NSF with these three linear GBCAs, clinical studies were performed in patients with CKD to assess the risk of NSF with group 2 GBCAs (Table 1). As noted, a recent systematic review of these studies concluded that the risk of NSF with group 2 GBCAs is essentially zero and formed the basis for recommendations that group 2 GBCAs can be administered to patients with severe CKD with essentially no concerns about NSF risk (3). Thus, pharmacologic (binding) differences in GBCAs are consistent with observed associations with NSF.

However, closer inspection of the clinical studies of group 2 GBCAs and NSF reveals some limitations. First, the number of patients at highest risk for NSF exposed to group 2 GBCAs is low, ranging from 170 to 2200 among the various group 2 GBCAs. The limited number of patients with CKD stage 5 or ESKD in these

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**Table 1. American College of Radiology classification of gadolinium-based contrast agent risk for nephrogenic systemic fibrosis**

American College of Radiology Group	Gadolinium-Based Contrast Agent	Structure	Binding Affinity Log $K_{\text{therm}}$
Group 1: Associated with greatest risk of NSF	Gadodiamide (Omniscan)	Linear, nonionic	16.9
	Gadoversetamide (OptiMARK)	Linear, nonionic	16.6
	Gadopentetate dimeglumine (Magnevist)	Linear, ionic	22.5
Group 2: Associated with few, if any, cases of unconfounded NSF	Gadobenate dimeglumine (Multihance)	Linear, ionic	22.6
	Gadobutrol (Gadavist)	Macrocyclic, nonionic	21.8
	Gadoteridol (Prohance)	Macrocyclic, nonionic	23.8
Group 3: Limited data regarding NSF risk	Gadoteric acid (Dotarem)	Macrocyclic, ionic	24.7
	Gadoxetate disodium (Eovist)	Linear, ionic	22.6

NSF, nephrogenic systemic fibrosis.

studies raises concerns about underpowering because NSF is fortunately an uncommon disease, with reported incidences of 4%–7% after exposure to group 1 GBCAs. Second, because of pharmacologic differences, it may not be appropriate to present all group 2 agents as having equivalent NSF risk. For example, many more cases of NSF have been reported with gadopentetate compared with gadobenate despite both being linear ionic GBCAs. Third, it is difficult to determine how much of the currently observed absence of NSF can be attributed to restrictive policies about GBCA exposure or more selective use of group 2 GBCAs in high-risk patients. Fourth, in these studies, patients had exposure to only one or two GBCA administrations at recommended doses. Thus, any conclusions about safety cannot be extended to patients who receive multiple GBCA injections or with doses that exceed manufacturer recommendations. Finally, for the most part, these studies were retrospective and primarily relied on electronic medical records to detect cases of NSF; although this method was probably sufficient to detect severe cases of NSF, milder NSF cases may have been missed. Despite these limitations, under the conditions of the studies, the risk of NSF in patients with severe CKD appears to be very low with group 2 GBCAs. However, the risk of NSF with group 2 agents is not zero as evidenced by a handful of reports describing patients who developed NSF after group 2 GBCA exposure (7). Furthermore, in experimental studies, group 2 GBCAs have been shown to have fibrogenic properties, although to a lesser extent than group 1 GBCAs.

The safety of GBCAs has further been confounded by observations, initially made in 2014 and subsequently confirmed, that patients exposed to GBCAs demonstrate evidence of T1 signal enhancement of the globus pallidus and dentate nuclei of their brains on unenhanced magnetic resonance (MR) imaging (8). In both autopsy and experimental studies,  $\text{Gd}^{+3}$  has been demonstrated in these brain anatomic areas after GBCA exposure, and the  $\text{Gd}^{+3}$  brain tissue concentrations correlate with T1 signal intensity. This phenomenon has been primarily reported with linear GBCAs and after multiple administrations. Clinical and experimental studies have shown T1 signal enhancement and  $\text{Gd}^{+3}$  brain deposition with macrocyclic GBCAs, although at

a magnitude far less than with linear GBCAs. Fortunately, there have been no adverse clinical consequences due to brain  $\text{Gd}^{+3}$  deposition (5). Nonetheless, because of concerns about this finding, several organizations have issued warnings about brain deposition and the United Kingdom Medicines and Healthcare Products Regulatory Agency suspended the licenses for some linear agents (gadodiamide and gadopentetic acid) and restricted the use of other linear GBCAs (gadobenate and gadoxetate) to hepatobiliary imaging only. Of greater concern is that clinical and experimental studies of T1 signal enhancement due to  $\text{Gd}^{+3}$  brain deposition have primarily been in patients and animals with normal renal function. Similar to observations of NSF, a greater potential for dissociation and brain deposition of  $\text{Gd}^{+3}$  in the presence of impaired renal function has been demonstrated in a limited number of clinical and experimental studies.

Another recently described potential consequence of GBCA exposure has been patient reports of symptoms of burning pain and paresthesias in the extremities, skin thickening, and clouded mentation after a GBCA-enhanced MR study. These symptoms have been termed gadolinium deposition disease (9). Because of the absence of controls and the subjective bias of patient symptoms, it is unclear if gadolinium deposition disease is a true clinical entity. Again, patients with impaired renal function have not been studied for this purported condition.

On the basis of the above, we offer the following nephrology perspective. We are in complete agreement with Soloff and Wang (5) that a GBCA-enhanced MR study when *medically necessary* should not be withheld in patients with severe CKD due to concerns of NSF or  $\text{Gd}^{+3}$  brain deposition. However, in such patients, physicians should *preferentially use* non-GBCA imaging modalities if they can provide diagnostic information that is comparable to the GBCA-enhanced MR study. Nephrologists who become aware that their patient is scheduled for a GBCA-enhanced MR study should discuss the benefits of GBCA enhancement and alternative non-GBCA imaging with a radiologist before endorsing the GBCA-enhanced MR study. In our experience, such discussions often lead to an unenhanced MR or an alternative imaging study being performed

without a loss of clinical benefit. Nephrologist should also be cautious about subjecting their patients to multiple exposures of GBCAs or studies using GBCAs at higher than recommended doses. Our recommendations concur with recommendations of the European Society of Urogenital Radiology, the Canadian Association of Radiology, and the Food and Drug Administration (10). The safety of GBCAs in patients with severely impaired renal function is an evolving story and new recommendations are likely as additional information comes forth.

#### Author Contributions

M. Rudnick wrote the original draft of the manuscript; A. Leonberg-Yoo and I. Wahba reviewed and edited the manuscript; and all authors conceptualized the study.

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