Gadolinium-based contrast agents (GBCAs) improve the diagnostic capabilities of magnetic resonance imaging. Although initially believed to be without major adverse effects, GBCA use in patients with severe chronic kidney disease (CKD) was demonstrated to cause nephrogenic systemic fibrosis (NSF). Restrictive policies of GBCA use in CKD and selective use of GBCAs that bind free gadolinium more strongly have resulted in the virtual elimination of NSF cases. Contemporary studies of the use of GBCAs with high binding affinity for free gadolinium in severe CKD demonstrate an absence of NSF. Despite these observations and the limitations of contemporary studies, physicians remain concerned about GBCA use in severe CKD. Concerns of GBCA use in severe CKD are magnified by recent observations demonstrating gadolinium deposition in brain and a possible systemic syndrome attributed to GBCAs. Radiologic advances have resulted in several new imaging modalities that can be used in the severe CKD population and that do not require GBCA administration. In this article, we critically review GBCA use in patients with severe CKD and provide recommendations regarding GBCA use in this population.

Introduction

Magnetic resonance (MR) imaging is based on the ability of hydrogen atoms to change their energy state when exposed to radiofrequency waves applied when subjected to a strong magnetic field, giving a measurable signal that can be used to probe tissue properties. Gadolinium is a lanthanide metal with paramagnetic properties that shortens the T1 and T2 relaxation times of water protons, increasing contrast between tissues and allowing improved diagnostic capability. Free gadolinium ion (Gd$^{3+}$) is highly toxic to tissues and to minimize this toxicity, Gd$^{3+}$ is combined with a chelating substrate. The first gadolinium-based contrast agent (GBCA) was approved for clinical use by the US Food and Drug Administration (FDA) in 1988, followed by the approval of 8 others. Each year, 30 million doses of GBCAs are administered and more than 450 million doses have been administered worldwide since their introduction.2

Following the introduction of GBCAs in clinical practice, there was a paucity of adverse safety events. However, in 2006, GBCAs were reported to play a pathogenetic role in a devastating condition termed nephrogenic systemic fibrosis (NSF). These reports led to regulatory warnings and restrictive policies about the use of GBCAs in patients with severe chronic kidney disease (CKD), resulting in a dramatic reduction in reported NSF cases.3

There are now multiple studies suggesting that GBCAs with high binding affinity for Gd$^{3+}$ have an extremely low NSF risk in patients with CKD and that restrictive policies avoiding GBCAs in patients with CKD are not applicable to these agents.4 This recommendation has been met with trepidation by many nephrologists, and there continues to be controversy about the safety and use of these GBCAs in patients with CKD. Uncertainties surrounding GBCA safety are further complicated by observations of Gd$^{3+}$ deposition in the brain and a possible clinical syndrome termed “gadolinium deposition disease.” In this article, we review multiple aspects of GBCA use in patients with CKD to provide physicians a comprehensive understanding of the unique issues relating to their use in this population.

Pharmacologic and Chemical Properties of GBCAs

GBCAs are categorized as linear or macrocyclic based on the type of chelate, a polyaminocarboxylate ligand that binds the Gd$^{3+}$, and by their charge as either ionic or nonionic (Table 1).5 Binding strength is measured in vitro under conditions simulating GBCAs in extra- and intracellular fluids and reported as thermodynamic and conditional stability constants (Table 1). These measurements demonstrate that macrocyclic GBCAs on average bind Gd$^{3+}$ tighter than linear GBCAs, and ionic GBCAs on average bind Gd$^{3+}$ tighter than nonionic GBCAs (Table 1).6 Release of free Gd$^{3+}$ can occur by a process called transmetallation, in which competing ions (specifically zinc, copper, and iron) displace Gd$^{3+}$ from the chelate. Transmetallation is a slow process and is unlikely to occur with rapid excretion of the GBCA by the kidneys. In the setting of decreased glomerular filtration rates (GFRs), the GBCA is retained longer, allowing time for transmetallation to occur. Transmetallation occurs more readily with linear GBCAs compared with macrocyclic because with the former, there is direct binding (and dissociation of free Gd$^{3+}$), whereas with the latter, there must first be an acid-catalyzed dissociation of the Gd$^{3+}$ from a macrocyclic ligand before the competing ion can bind.6

Nephrogenic Systemic Fibrosis

In 2000, Cowper et al described a series of 15 hemodialysis patients who developed extensive thickening and
### Table 1. Chemical and Pharmacologic Properties of Gadolinium-Based Contrast Agents

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Structure</th>
<th>Ionicity</th>
<th>Thermodynamic Stability (log $K_{\text{therm}}$)</th>
<th>Conditional Stability (log $K_{\text{cond}}$)</th>
<th>Concentration, mmol/mL</th>
<th>Dose</th>
<th>Half-Life, h*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>pH 7.4: 14.9</td>
<td>pH 4.0: 10.8</td>
<td>0.5</td>
<td>0.1 mmol/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.3 ± 0.25</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>Linear</td>
<td>Nonionic</td>
<td>16.9</td>
<td>pH 7.4: 15.0</td>
<td>0.5</td>
<td>0.1 mmol/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 10.9</td>
<td></td>
<td></td>
<td>1.72 ± 0.3</td>
</tr>
<tr>
<td>Gadoversetamide (OptiMARK)</td>
<td>Linear</td>
<td>Nonionic</td>
<td>16.6</td>
<td>pH 7.4: 15.0</td>
<td>0.5</td>
<td>0.1 mmol/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 10.9</td>
<td></td>
<td></td>
<td>1.6 ± 0.13</td>
</tr>
<tr>
<td>Gadopentetate (Magnevist)</td>
<td>Linear</td>
<td>Ionic</td>
<td>22.5</td>
<td>pH 7.4: 18.4</td>
<td>0.5</td>
<td>0.1 mmol/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 11.2</td>
<td></td>
<td></td>
<td>1.17-1.6</td>
</tr>
<tr>
<td>Gadoxetate (Primovist, Eovist)</td>
<td>Linear</td>
<td>Ionic</td>
<td>23.5</td>
<td>pH 7.4: 18.7</td>
<td>0.25</td>
<td>0.025 mmol/kg</td>
<td>0.1 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 11.5</td>
<td></td>
<td></td>
<td>1.1-1.6</td>
</tr>
<tr>
<td>Gadobenate (MultiHance)</td>
<td>Linear</td>
<td>Ionic</td>
<td>22.6</td>
<td>pH 7.4: 18.4</td>
<td>0.5</td>
<td>0.1 mmol/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 11.1</td>
<td></td>
<td></td>
<td>1.17-2.02</td>
</tr>
<tr>
<td>Gadofosveset (Vasovist, Ablavá)</td>
<td>Linear</td>
<td>Ionic</td>
<td>22.1</td>
<td>pH 7.4: 18.9</td>
<td>0.25</td>
<td>0.03 mmol/kg</td>
<td>0.12 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 11.6</td>
<td></td>
<td></td>
<td>16.3 ± 2.6</td>
</tr>
<tr>
<td>Gadoteridol (ProHance)</td>
<td>Macroyclic</td>
<td>Nonionic</td>
<td>23.8</td>
<td>pH 7.4: 17.1</td>
<td>0.5</td>
<td>0.1 mmol/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 9.9</td>
<td></td>
<td></td>
<td>1.57 ± 0.08</td>
</tr>
<tr>
<td>Gadobutrol (Gadoviast)</td>
<td>Macroyclic</td>
<td>Nonionic</td>
<td>21.8</td>
<td>pH 7.4: 16.1</td>
<td>1.0</td>
<td>0.1 mmol/kg</td>
<td>0.1 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 9.0</td>
<td></td>
<td></td>
<td>1.81 ± 2.4</td>
</tr>
<tr>
<td>Gadoterate (Dotarem)</td>
<td>Macroyclic</td>
<td>Ionic</td>
<td>24.7</td>
<td>pH 7.4: 17.2</td>
<td>0.5</td>
<td>0.1 mmol/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pH 4.0: 3.5</td>
<td></td>
<td></td>
<td>1.4-2.0</td>
</tr>
</tbody>
</table>

*Note: $K_{\text{therm}}$ is measured at a pH ~11, at which there are no competing hydrogen ions for the chelate and thus reflects a theoretical maximal stability for the GBCA. $K_{\text{cond}}$ is measured at either the physiologic pH of 7.4 or pH of 4. At pH of 4 (which can be seen in some intracellular environments), the conditional stability constant declines significantly due to the high concentration of competing hydrogen ions for the chelate. Binding strength is measured in vitro by the thermodynamic and conditional stability constants ($K_{\text{therm}}$ and $K_{\text{cond}}$), with higher values reflecting greater binding. Measurements of $K_{\text{therm}}$ and $K_{\text{cond}}$ demonstrate that macrocyclic GBCAs bind gadolinium tighter than linear GBCAs and that ionic GBCAs bind gadolinium tighter than nonionic GBCAs.2,6 The $K_{\text{cond}}$ of available GBCAs is in the range of $10^{15}$ to $10^{19}$, which means a solution of 1 mmol/L of GBCA contains 3 nmol/L to 10 pmol/L of free Gd$^{3+}$.8

Abbreviation: GBCA, gadolinium-based contrast agent; GFR, glomerular filtration rate (in mL/min/1.73 m$^2$); $K_{\text{cond}}$, conditional stability constant; $K_{\text{therm}}$, thermodynamic stability constant. Based on data from McDonald et al,2 Le Fur and Caravan,6 and Port et al.7

*Half-life data from US Food and Drug Administration package insert.

Hepatobiliary elimination, 50%.

Hepatobiliary elimination, 0.6%-4.0%.
hardening of the skin with histopathologic features of haphazardly arranged dermal collagen bundles and an increased number of fibroblast cells. This new skin abnormality was termed nephrogenic fibrosing dermopathy. After recognition that other organs may be involved, including heart, lung, gastrointestinal tract, central nervous system, kidneys, skeletal muscle, and diaphragm, the disease was renamed NSF.3,10 The lesions of NSF are usually symmetrical, develop on the limbs and trunk, and begin as a papule (skin colored or erythematous) that transitions to erythematous plaques with a peau d’orange appearance.11 Skin in these sites becomes thickened with a woody texture (Fig 112). Joint contractures commonly develop (Fig 213). Patients with NSF typically report burning, itching, and sharp pain in the involved areas, along with loss of mobility.11

The cause of NSF remained unknown until 2006, when 2 reports described patients receiving dialysis who developed NSF shortly after exposure to the GBCA gadodiamide.14,15 In 2007, Gd3+ deposition was found in areas of skin fibrosis in patients with NSF.16 Since then, multiple observations have demonstrated that virtually all NSF cases are associated with GBCA exposure. The role of Gd3+ in the causation of NSF has been further strengthened by numerous experimental studies,17-19 although there are some reports to suggest that the intact GBCA may itself be profibrotic.18

A systematic review identifying 639 patients with biopsy-proven NSF demonstrated that 75.8% were exposed to gadodiamide, and 12.1%, to gadopentetate dimeglumine, both linear GBCAs.3 The median interval between GBCA exposure and development of NSF was 42 (interquartile range, 19-90) days. In patients for whom data were available, 93.3% received a GBCA dose greater than the standard, and almost 30% of patients had multiple exposures. Importantly, 86.3% of patients were receiving dialysis at time of GBCA exposure, with one-fifth having acute kidney injury (AKI) requiring kidney replacement therapy. Among patients not receiving dialysis at the time of exposure, mean estimated GFR was 14.3 ± 8 mL/min/
1.73 m². Follow-up data demonstrated that 21% had partial and 3.5% had complete remission. In patients with remission, 40% occurred after restoration of kidney function. The clinical course was stable in 75% and progressive in 25%, and 4 deaths were attributed to NSF. The prevalence of NSF in patients with CKD GFR category 5 (G5) and those treated by dialysis (G5D) who are exposed to nonionic linear GBCAs is 3% to 7%. Only a minority of patients with severe CKD (CKD G4-G5 and dialysis dependent) or AKI who are exposed to GBCAs will develop NSF, suggesting that other factors (eg, edema, proinflammatory state, hyperphosphatemia, and erythropoiesis-stimulating agents) likely contribute to its development, although none are uniformly present.

The diagnosis of NSF can be challenging due to the rarity of the disease, similarity of presentation to other diseases, and absence of a pathognomonic clinical feature or laboratory study. An objective standardized clinicopathologic definition has been developed, including both clinical and histopathologic findings that are combined to improve the diagnostic accuracy.

There is no uniformly successful treatment for NSF, although a number of therapies have been tried with limited success. The most common treatments are extracorporeal photopheresis and imatinib mesylate. Resolution of NSF has been reported after recovery of AKI or following kidney transplantation, although not all transplant recipients demonstrate improvement.

As a result of reports linking NSF to GBCA exposure, in 2007, the FDA issued a black box warning of this risk, and in 2010, updated this to include that gadodiamide, gadopentetate, and gadoversetamide should not be used in patients with AKI or CKD G4-G5 or on dialysis. At the present time, a black box warning remains in place for all GBCAs, along with a recommendation that GBCAs should be avoided in patients with CKD G4-G5 or on dialysis unless the diagnostic information is essential and not available with noncontrast MR imaging or other modalities. Recently, FDA approval of gadopentetate and gadoversetamide was withdrawn at the request of the manufacturers.

**Clinical Studies of NSF With GBCAs With High Gadolinium Binding Affinity**

Following FDA warnings about the association of NSF with GBCAs, reports of NSF have dramatically diminished, likely due to adoption of restrictive policies on use in at-risk patients and more selective use of GBCAs with high-affinity binding for Gd. However, it is difficult to determine the relative contribution of each of these to the observed reduction in NSF cases. A number of studies evaluating the risk for NSF with GBCAs that have high-affinity Gd binding have now been published, demonstrating essentially no cases in patients with CKD G4-G5 or on dialysis. Detailed summaries of these studies for each GBCA formulation are presented in Tables S1 to S5. Each GBCA formulation is presented in its own table because one cannot assume a priori that all are of equivalent NSF risk given differences in thermodynamic binding and other chemical properties. For instance, substantially more...
Table 2. Group II GBCA Studies Evaluating Nephrogenic Systemic Fibrosis Risk in Patients With CKD or on Dialysis

<table>
<thead>
<tr>
<th>GBCA</th>
<th>No. of GBCA Administrations</th>
<th>No. of NSF Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoteridol</td>
<td>172</td>
<td>0</td>
</tr>
<tr>
<td>Gadobenate</td>
<td>2,306</td>
<td>0</td>
</tr>
<tr>
<td>Gadoterate</td>
<td>712</td>
<td>2</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>356</td>
<td>0</td>
</tr>
<tr>
<td>Gadoxetate</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,645</strong></td>
<td></td>
</tr>
</tbody>
</table>

Note: In some studies, patients with CKD G4 and G5 grouped together42,49,50,56-62; thus, this table overstates actual numbers of at-risk patients. For example, for the 356 participants in gadobutrol studies, 244 were from studies in which CKD G4 and G5 were reported together.42,50,56-62 They are listed in this table, although most of these 244 are likely to be CKD G4.

Abbreviations: CKD, chronic kidney disease; GBCA, gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

GSF cases have been reported with gadopentetate than gadobenate, although they are both linear ionic GBCAs. The studies summarized in Tables S1 to S5 have a number of limitations; they are all observational and mostly retrospective. Although collectively a large number of patients were evaluated, the number with CKD G5 or on dialysis was limited; this is important because ~90% of patients with NSF are such patients,3,20 with less-severe stages (CKD ≤ G4) having minimal risk. The relatively small number of patients with CKD G5 on dialysis among the different GBCA formulations (ranging from 99 to 2,306, as shown in Table 2) will reduce the precision of incidence rate estimates. In addition, most patients in these studies received only 1 to 2 exposures to a GBCA and at recommended doses. Thus, any conclusions about minimal/absent risk for NSF from these studies cannot be extended to patients who require multiple GBCA exposures or who receive higher than the recommended dosages. Another limitation in many of these studies is that NSF detection was based on patient self-reporting or electronic medical record review. Although these methods are likely to detect severe cases of NSF, more limited forms of NSF may have been missed. Even so, the data appear to support the conclusion that the risk for NSF in patients with CKD G4-G5 and in dialysis patients following the administration of GBCAs with high Gd³⁺ binding affinity under conditions (dose and frequency) in these studies is extremely low. Despite these favorable clinical reports, experimental studies of NSF have compared linear (low binding affinity) versus macrocyclic (high binding affinity) GBCAs, finding detectable Gd³⁺ in the skin and an increase in markers of fibrogenesis with both types, although these findings are much more pronounced with linear GBCAs64-68 and in the presence of decreased GFR.69

Based on these reports and other observations, the American College of Radiology classifies GBCAs into 3 groups determined by the GBCA association with NSF (Box 1). Group I agents are those associated with the greatest number of reported cases, and group II agents are associated with few if any unconfounded cases of NSF. This classification correlates with measured Gd³⁺ binding strengths of the different GBCAs (Table 1).

NF Reports Following Exposure to GBCAs With High Binding Affinity for Gadolinium

Despite these clinical studies, there are a few reports of NSF after exposure to group II GBCAs.71-75 Bayer, a GBCA manufacturer, published an article with all purported cases received by their Pharmacovigilance Department between 2006 and 2016.76 There were 563 NSF reports in which gadopentetate (group I GBCA) was given either as the sole or one of several GBCAs administered. These reports contained 16 cases in which a group II GBCA was also given; the elapsed time between administration of gadopentate and onset of NSF symptoms varied from 3 months to 9 years, whereas the time from exposure to the group II GBCA to onset of NSF symptoms ranged from less than 1 to 11 months. Because NSF usually presents within a few months after GBCA exposure, these observations are concerning for a pathogenetic role of group II GBCAs. There were an additional 5 patients who had received the group II GBCA gadobutrol as the sole GBCA, of whom 3 were determined to be consistent with or diagnostic of NSF. This report provides evidence that gadobutrol can be associated with NSF and the temporal associations suggest that group II GBCAs may cause NSF despite these cases being confounded with a group I GBCA.

FDA Reports of NSF

Cases of suspected NSF continue to be reported to the FDA (Fig 3), with 3,120 reported through 2019.77 Most of these were with group I GBCAs. As demonstrated in Table 3, the FDA has also received 46 unconfounded reports of NSF with group II GBCAs. Multiple sources including clinicians, manufacturers, and patients provide reports to the FDA; these reports may lack detail in determining causality. Because we did not review the detailed individual unconfounded reports in Table 3, it is unknown how many contain histopathology and other clinical findings consistent with NSF. Given the multiple limitations inherent in FDA adverse events reports, the reporting of unconfounded cases with group II GBCAs requires further investigation but raises a concern that the occurrence of NSF with group II GBCAs may not be zero.
Gadolinium Bone and Brain Deposits, Gadolinium Storage Disease, Gadolinium Deposition Disease, and Gadolinium Plaques

Bone Deposition

Gadolinium bone deposition occurs with both linear and macrocyclic GBCAs (levels higher with linear) and is seen in individuals with normal GFRs.66,78 Whether excess Gd\(^{3+}\) deposition in bone can result in pathologic conditions or act as reservoirs that release Gd\(^{3+}\) to cause toxicity elsewhere in the body remains unknown.

Brain Deposition

In 2014, Kanda et al79 were the first to demonstrate high signal intensity on unenhanced T1-weighted MR images in the dentate nucleus and globus pallidus areas of the brain in patients with normal GFR who had a history of multiple GBCA exposures. Autopsy studies of patients who have undergone multiple GBCA-enhanced studies demonstrate increased Gd\(^{3+}\) levels in the dentate nucleus and globus pallidus.80 Unenhanced T1 signal intensity occurs primarily with exposure to linear compared with macrocyclic GBCAs,81 although repeat injections of macrocyclics can also cause this finding.82 Most patients reported who developed unenhanced T1 signal hyperintensity after GBCA administrations had normal GFRs; however, concerns about Gd\(^{3+}\) brain deposition should be greater in patients with decreased renal clearance, similar to the occurrence of NSF. In the few studies comparing hemodialysis patients with individuals with normal GFR, the frequency and intensity of T1 signal enhancement after exposure to linear GBCAs was significantly greater in hemodialysis patients.83

At the present time, there do not appear to be any clinically relevant adverse effects or histopathologic abnormalities from Gd\(^{3+}\) deposition in humans, although experimental studies have demonstrated toxicity in cultured human neurons.84 In 2017, the FDA issued a statement requiring labeling that all GBCAs can result in long-term Gd\(^{3+}\) brain deposition.85 In response to these findings, the UK Medicines and Healthcare Products Regulatory Agency recommended that licenses be suspended for the linear agents gadodiamide and gadopentetic acid, whereas use of gadobenate meglumine and gadoxetate be limited to liver imaging.86 In addition to these recommendations, we would add that because the impact of group II GBCAs on brain deposition in patients with CKD G4-G5 and dialysis patients has to date been only minimally evaluated, even greater caution should be exercised in these patients with respect to the potential for any adverse neurologic effects, and if GBCA administration is necessary, macrocyclic formulations are preferred.

Gadolinium Storage Disease, Gadolinium Deposition Disease, and Gadolinium Plaques

Gd\(^{3+}\) deposition in humans has now been detected in multiple organs following GBCA administration, and this systemic deposition has been termed gadolinium storage condition.87 Anonymous patient responses in an online survey posted inquiring about symptoms within 1 year of GBCA exposure included a glove and stocking distribution of burning pain or pins and needles sensation, skin thickening and discoloration, bone pain, joint stiffness, muscle spasms, metallic taste, and clouded mentation (“brain fog”), termed gadolinium deposition disease.87,88 The prevalence of this condition, as well as the causal GBCA relationship, remains unclear due to study limitations, including selection bias and absence of a control group. In addition, there are reports of patients who developed skin plaques after GBCA exposure, termed gadolinium-associated plaques, but who did not have classic NSF findings.89

Table 3. FDA Received Cases of NSF of Group II GBCA Formulations Unconfounded/Confounded

<table>
<thead>
<tr>
<th>GBCA</th>
<th>Total Reports</th>
<th>Unconfounded</th>
<th>Confounded</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadobenate</td>
<td>584</td>
<td>13</td>
<td>3</td>
<td>568</td>
<td></td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>582</td>
<td>7</td>
<td>5</td>
<td>570</td>
<td></td>
</tr>
<tr>
<td>Gadoterate</td>
<td>44</td>
<td>18</td>
<td>5</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>24</td>
<td>7</td>
<td>2</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Gadoxetate</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, US Food and Drug Administration; GBCA, gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.
Imaging Without Gadolinium

MR Angiography Without GBCAs

Techniques (such as time-of-flight and phase-contrast) for MR angiography imaging of the vasculature without the use of GBCAs have been available for many years but are limited by low spatial resolution, prolonged imaging time, and flow artifacts. Newer unenhanced MR techniques, including steady-state free-precision, arterial spin labeling, and quiescent interval slice-selective acquisitions, have improved diagnostic accuracy by suppression of background signals, short acquisition times, and use of cardiac and respiratory synchronization to reduce motion artifacts. Of interest to nephrologists, these new techniques show excellent correlation with GBCA-enhanced MR angiograms for visualization of renal arteries, grading of renal artery stenosis, and evaluation of vascular abnormalities in kidney transplant recipients.

Ferumoxytol as an MR Contrast Agent

Superparamagnetic iron oxide nanoparticles such as ferumoxytol (Feraheme [AMAG Pharmaceuticals]) have been investigated “off-label” as possible alternatives to GBCAs in MR imaging. Ferumoxytol is a blood pool agent and is retained in the vasculature longer than GBCAs, resulting in less soft tissue enhancement than traditional GBCAs, thus producing less obstructed views of blood vessels. Ferumoxytol has been evaluated for aortic aneurysms, pulmonary embolism, aortic dissection, intracranial aneurysms, arteriovenous fistulas, coronary and carotid arteries, renal artery stenosis, and kidney transplant vascular abnormalities.

Contrast-Enhanced Ultrasounds

Contrast-enhanced ultrasonography is a relatively new technique that is of value in the evaluation of a renal mass, although this is an off-label use of this technology. Contrast agents in contrast-enhanced ultrasonography are microbubbles composed of gas (air, nitrogen, and perfluorocarbon) surrounded by a stabilizing biomaterial shell (galactose, lipids, protein, and polymers), poorly soluble in blood, and eliminated by the lungs, with no renal clearance or nephrotoxic potential. Microbubbles increase the number of sonographic reflections within vessels, producing acoustical characteristics that differ from the surrounding medium. In patients with CKD, the sensitivity of contrast-enhanced ultrasonography for detecting malignant renal lesions is 90% to 100%, with specificity of 70% to 99%.

Nephrotoxicity of GBCAs

In the past, the practice of substituting iodinated contrast media with GBCAs in arteriography or computed tomography in patients with CKD was common, given concerns for iodine contrast–associated AKI coupled with a belief that GBCAs did not cause AKI. However, when GBCA-induced NSF became recognized, this practice fell out of favor. Given recent assessments that the risk for NSF with group II GBCAs is extremely low, the use of GBCAs instead of iodinated contrast may again become an attractive alternative. Initial and contemporary reports indicate that GBCAs are not nephrotoxic in doses up to 0.4 mmol/kg in patients with normal and abnormal GFRs. Nevertheless, nephrotoxicity attributed to GBCAs has been reported, with some requiring temporary hemodialysis.

Ferumoxytol, an iron oxide nanoparticle, has been evaluated for aortic aneurysms, pulmonary embolism, aortic dissection, intracranial aneurysms, arteriovenous fistulas, coronary and carotid arteries, renal artery stenosis, and kidney transplant vascular abnormalities.

The potential for GBCA nephrotoxicity is limited to patients who receive high GBCA doses required to achieve adequate imaging when GBCAs are substituted for iodine contrast. At equal attenuating doses, there is little support for less nephrotoxicity with GBCAs compared with iodinated contrast media.

Safe administration of GBCAs to patients with severely decreased GFRs has been discussed widely since the observation in 2006 that these agents, primarily group I GBCAs, are associated with NSF. The implementation of restrictive policies on GBCA administration to patients with CKD G4–G5 and dialysis patients or AKI has resulted in a dramatic reduction of observed NSF cases. However, these policies are likely to prevent clinical benefit to patients when an enhanced MR study is the best diagnostic option. More recent clinical and experimental studies demonstrate that group II GBCAs have an extremely low risk for causing NSF in patients with severely decreased GFRs and thus should be administered to these patients if clinically indicated. Despite these observations, many nephrologists continue to be concerned about the safety of GBCA administration in patients with severely decreased GFRs. The safety of GBCAs in patients with decreased GFRs is further complicated by more recent observations of brain deposition of gadolinium and the possibility that exposure may cause a systemic disease, termed gadolinium deposition disease.

These continuing concerns about GBCA exposure in patients with severely decreased GFRs are not without merit. The safety of group II GBCAs has been demonstrated in studies limited by relatively small numbers of patients with severely decreased GFRs and thus likely underpowered, and who have been exposed to 1 or a few administrations at doses that do not exceed recommendations. It remains uncertain what the risk for NSF would be if GBCAs...
again are frequently administered to patients with severely decreased GFRs.

Based on this review, the authors make the following recommendations. Administration of GBCAs to patients with severely decreased GFRs should be done with caution. Before GBCA administration, physicians should determine whether non-GBCA imaging modalities can provide similar diagnostic information and if so, they should be used. Nephrologists who become aware that a GBCA-enhanced MR study has been ordered in their patients should discuss with the radiologist the benefit of contrast enhancement and the value of non-GBCA imaging studies. In the absence of a non-GBCA imaging alternative, patients should not be denied enhanced MR study if clinically beneficial. In such cases, macrocyclic GBCAs at recommended doses should be used. Multiple GBCA-enhanced MR studies and doses that exceed recommended amounts should be avoided if possible. In hemodialysis patients, we recommend prompt hemodialysis following GBCA exposure. GBCAs should not be substituted for iodine contrast in radiology imaging and physicians should be aware that GBCAs possess nephrotoxic potential at high doses. These recommendations are consistent with those made by multiple professional societies (Box 2). The safety of GBCA administration in general and especially in patients with decreased GFRs is an evolving story and recommendations are likely to change as more information and/or new non-gadolinium-containing MR contrast agents become available.

Box 2. Society Recommendations for GBCA Use in Patients at Risk for NSF: CKD G5-G5D and AKI

**American College of Radiology**
- Recommended GBCAs: gadobenate, gadobutrol, gadovist, gadoterate, gadoteridol (group 2 GBCAs)
- Contraindicated GBCAs: gadodiamide, gadopentetate, gadoversetamide, gadoxetate (group 1 and 3 GBCAs)
- Use lowest dose to obtain needed clinical information; do not exceed recommended single dose
- CKD screening and informed consent for group 2 GBCAs not necessary; deference made to local practice preference
- In patients with ESKD who are anuric and without residual renal function, reasonable to perform contrast-enhanced CT instead of GBCA MR if diagnostic yield similar
- For maintenance dialysis patients, perform GBCA MR study as closely before hemodialysis as possible; repeat dialysis sessions are not necessary
- No special precautions regarding GBCA choice are needed for CKD stages 1-3

**Canadian Association of Radiology**
- Patients at risk for NSF should receive GBCA-enhanced MR study only when medically indicated and non-GBCA-enhanced imaging modalities are not suitable alternatives
- Recommended GBCAs: ACR group 2 GBCAs and gadoxetate
- Contraindicated: group 1 GBCAs
- Screening for CKD not required; informed consent not necessary; screen in-patients for AKI
- Caution against high-dose GBCA-enhanced MR studies; for multiple GBCA MR studies, allow sufficient time between procedures for GBCA elimination
- Perform hemodialysis 2-3 h after GBCA only for patients already receiving hemodialysis; repeat hemodialysis sessions outside usual schedule not necessary
- Monitor patients for symptoms and signs of NSF for 2 y after GBCA exposure
- No special precautions regarding GBCA choice are needed for CKD stages 1-3

**European Society of Urogenital Radiology**
- European Medicines Agency has suspended intravenous use of gadodiamide, gadopentetate, gadoversatimide
- Gadobenate and gadoxetate approved for hepatobiliary imaging only
- Gadobutrol, gadoterate, and gadoteridol should be used with caution in patients with eGFR < 30 mL/min/1.73 m²
- Limit GBCA exposure to less than once every 7 d and administer lowest possible dose
- Laboratory testing of renal function not mandatory and if not performed, questionnaire sufficient

**Supplementary Material**

**Supplementary File (PDF)**
- Table S1: Gadoteridol NSF studies.
- Table S2: Gadoterate NSF studies.
- Table S3: Gadobenate NSF studies.
- Table S4: Gadobutrol NSF studies.
- Table S5: Gadoxetate NSF studies.

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