

A REVIEW OF GADOLINIUM-BASED CONTRAST AGENTS IN MAGNETIC RESONANCE IMAGING

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INTRODUCTION

Magnetic resonance imaging (MRI) is a valuable non-invasive imaging modality that provides high-resolution, three-dimensional images of internal structures. Compared to computed tomography (CT), MRI offers better contrast between various soft tissues of the body. Because MRI offers information on anatomy, function, and metabolism of tissues, it is especially useful in neurological (brain), musculoskeletal, cardiovascular, and oncology imaging.¹ However, unlike CT, MRI uses no ionizing radiation. Additionally, the contrast agents used in MRI are less likely to be nephrotoxic or to cause an allergic reaction, compared to the iodinated contrast agents used in CT.²

MRI is a relatively recent technology; the first studies on a living human being were published in 1977.³ Basically, MR imaging is the visualization of hydrogen atoms in free water and in organic macromolecules (i.e., lipids and proteins). In simple terms, this technology is based on the response of the body's hydrogen atoms (protons) to a magnetic field that receives a pulse from a radio-frequency (RF) transmitter. First, the magnetic field causes the hydrogen atoms, which behave like bar magnets, to align themselves along the magnetic field. They are not stationary, and they don't align themselves perfectly in this external magnetic field; they continue to rotate in place (in a cone-shaped fashion). The frequency of this rotation, termed *precession*, is dependent on the strength of the magnetic field. An applied radio-frequency pulse adjusted to the same frequency of precession alters the alignment of the protons in this magnetic field from a longitudinal to a

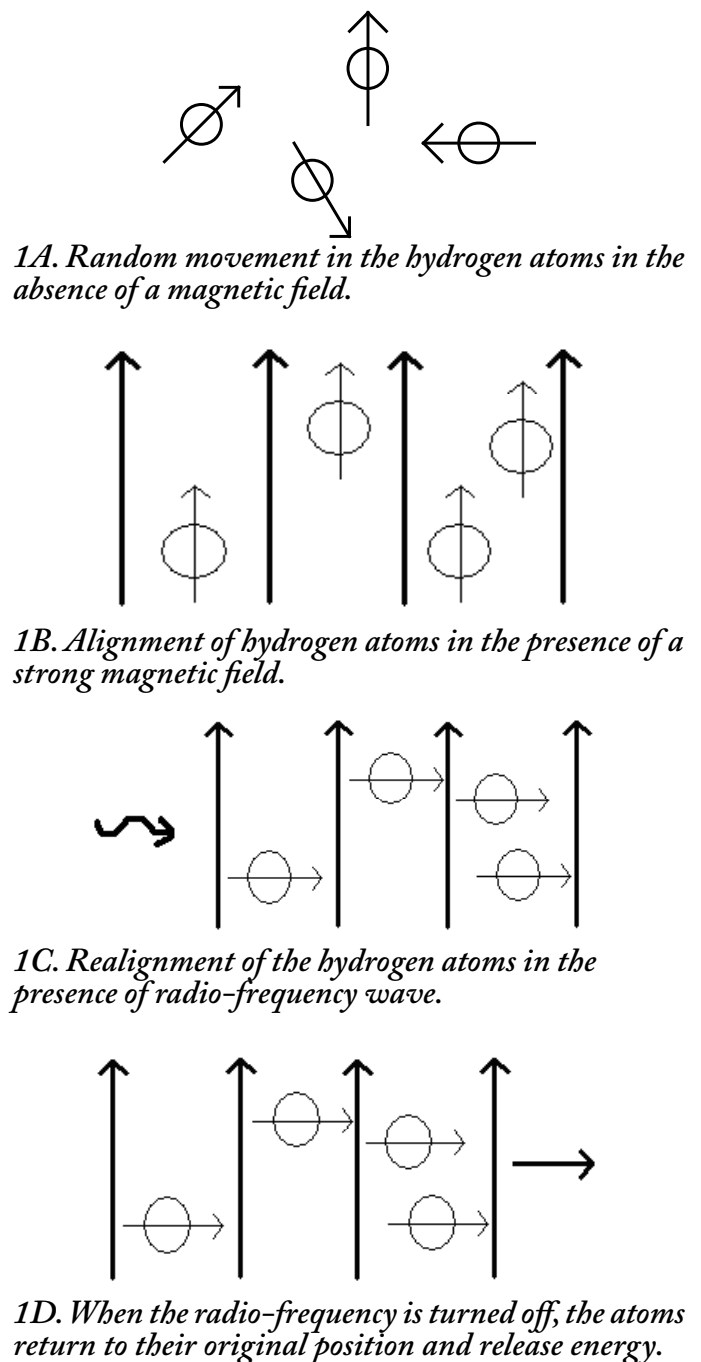


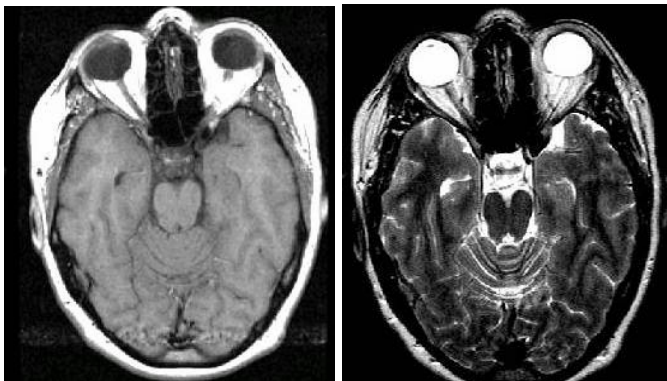
FIGURE 1. A Representation of the Behavior of Hydrogen Atoms Exposed to an External Magnetic Field Exposed to a Radio-Frequency Pulse

perpendicular (or transverse) axis. This alteration can be measured. After the RF pulse, the hydrogen atoms recover back to their original state (Figure 1).

This recovery in both the longitudinal and transverse magnification is termed *relaxation*. The time it takes after an RF pulse for the tissue to recover to its original longitudinal magnetic field is termed T1 (or spin-lattice relaxation). The time it takes after an RF pulse for the relaxation of the transverse magnetization to dissipate is termed T2 (or spin-spin relaxation). T1 and T2 values vary depending on the tissue type; for example, water has a relatively long T1 and T2 compared to fat, which has a relatively short T1 and T2. The RF pulse-induced alterations in transverse and longitudinal magnetic fields are detected by an antenna system housed within the scanner and converted into an image. By applying specifically designed sequences of RF pulses, the MR operator can vary the image to emphasize the characteristics of a particular tissue.² The appearance of T1- and T2-weighted images will differ depending on the tissue type being studied (Table 1).

TABLE 1. A Comparison of T1- and T2-weighted Images

Substance	T1-weighted	T2-weighted
Water/Vitreous/CSF	Black	Light grey or white
Fat	White	Light grey
Muscle	Grey	Grey
Air	Black	Black
Fatty bone marrow	White	Light grey
White brain matter	Light grey	Grey
Grey brain matter	Grey	Very light grey



From the Royal College of Ophthalmologists⁴

BENEFITS OF MRI

The benefits of MRI have been discussed in several CEwebsource.com articles. It is clear from these papers that MRI is now considered to be the preferred imaging

method for providing high-detailed images of musculo-skeletal abnormalities, cardiac tumors,⁵ anatomy of the heart and coronary arteries,⁶ and acute stroke.⁷

A recent study demonstrated that MRI has a distinct advantage over standard radiography in an emergency department for detecting hip and pelvic fractures.⁸ In this retrospective study, radiographs and MR images (at Duke University) from 2005 through 2008 were reviewed and compared. Using MRI, fractures were found in 14% of patients with normal radiographic findings. Conversely, in 12% of patients with radiographs suggesting a fracture, MRI showed no fracture. In a majority of patients (73%), MRI was able to confirm the absence of a fracture and to identify the source of pain, including muscle edema and tears, trochanteric bursitis, and hamstring tendinopathy.

GADOLINIUM-BASED CONTRAST AGENTS

Under most conditions, tissue proton spin density and the longitudinal (T1) and transverse (T2) relaxation times are usually high enough to provide sufficient contrast for quality MR images; however, some pathological conditions do not display specific enough changes in relaxation times to differentiate them from surrounding healthy tissue. In these cases, MRI contrast agents that alter the local relaxation times of tissue have been shown to improve detection of pathological tissue. This combination of MRI and contrast agents has improved our ability to visualize a variety of disease states, including inflammation (arthritis), tumor angiogenesis, atherosclerosis, and multiple sclerosis. Gadolinium-based contrast agents (GBCAs) have been successfully used to enhance MR images by affecting both T1 and T2 relaxation times, providing a stronger MR signal and a brighter image.¹

Gadolinium is a paramagnetic trivalent lanthanide cation (Gd^{3+}) that is highly toxic as a free ion because it competes with calcium. Because gadolinium has a higher binding affinity for calcium-binding enzymes, it displaces calcium and alters all biological processes catalyzed by these enzymes.⁹ Free gadolinium ions interfere with a variety of calcium-related enzymes, including Ca^{2+} -activated Mg-adenosine triphosphatase (ATPase) dehydrogenases, kinases, glutathione S-transferases, and aldolase, due to its noncompetitive inhibition of Ca^{2+} binding.¹⁰ Free gadolinium also interferes with calcium channels to block physiological pathways that rely on Ca^{2+} influx (i.e., neural transmission and coagulation).¹⁰ When bound (or chelated) to an organic ligand, gadolinium is generally regarded as safe for use as an MRI contrast agent. Chelation also improves water solubility.¹¹

Currently, there are nine GBCAs approved for use in the United States and/or the European Union (Table 2).⁹ Seven of these are approved for use in the United States:

gadobenate disodium (MultiHance), gadodiamide (Omniscan), gadopentetate dimeglumine (Magnevist), gadobutrol (ProHance), gadoversetamide (Optimark), gadoxetate disodium (Eovist, also known as Primovist), and gadofosveset trisodium (Ablavar, previously known as Vasovist).¹²

TABLE 2. Chemical, Generic, and Product (Trade) Names for Gadolinium-Based Contrast Agents Approved for Use in the United States of America and/or the European Union

Generic Name	Product/Trade Name
Gadopentetate dimeglumine	Magnevist
Gadoterate meglumine	Dotarem
Gadodiamide	Omniscan
Gadoteridol	ProHance
Gadobutrol	Gadovist
Gadoversetamide	Optimark
Gadobenate disodium	MultiHance
Gadoxetate disodium	Primovist/Eovist
Gadofosveset trisodium	Vasovist/Ablavar

Most available GBCAs that shorten the T1 relaxation time to enhance MR images are low-molecular-weight polyamino-carboxylate compounds.¹ They can be classified on the basis of their binding to serum albumin,¹¹ their biochemical structures (macrocyclic vs linear), or their ionicity (ionic vs nonionic).¹³

The pharmacokinetics of most GBCAs are also similar. They are water soluble, are distributed in the extra-

cellular spaces, are not metabolized, and are excreted unchanged by the kidneys. There are exceptions, though. Gadoxetate disodium enters liver cells and is excreted in both feces and urine. This GBCA has been used successfully to enhance MRI of the liver. Circulating gadofosveset is 80% to 90% bound to serum albumin and has been successfully used as a blood pool agent due to its longer intravascular duration. A small portion of circulating gadobenate is also bound to serum protein; however, it is taken up by liver cells and approximately 4% is excreted in the feces. Other than gadobenate and gadofosveset, GBCAs are not protein-bound or excreted in feces (Table 3).¹¹

TABLE 3. Summary of GBCA Binding to Serum Albumin

No binding
Gadopentetate diglumine
Gadodiamide
Gadoteridol
Gadoversetamide
Gadoxetate disodium
Weak binding
Gadobenate disodium
Strong reversible binding
Gadofosveset trisodium

In patients with normal renal function, the half-life of GBCAs is approximately 1.5 hours and 90% is excreted after 24 hours.¹¹ Molecular weights of GBCAs vary from 559 to 1058 Daltons (Table 4).

TABLE 4. Characteristics of GBCAs^{11,13}

Generic name	Osmolality, 37°C, osmol/kg H ₂ O	Viscosity, mPa 20°C	Viscosity, mPa 37°C	Molecular Weight	Charge	Structure
Gadopentetate	1.96	4.9	2.9	939.0	Ionic	Linear
Gadodiamide	0.79	2.0	1.4	573.6	Nonionic	Linear
Gadoteridol	0.63	2.0	1.3	558.7	Nonionic	Cyclic
Gadoversetamide	1.11	3.1	2.0	661.8	Nonionic	Linear
Gadoxetate	0.688	-	1.19	682.0	Ionic	Linear
Gadobenate	1.97	9.2	5.3	1058.2	Ionic	Linear
Gadofosveset	0.825	3.0	1.8	958.0	Ionic	Linear

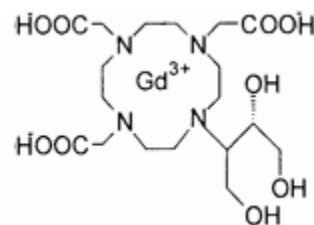
GBCAs also vary with respect to osmolality and viscosity. Imaging quality variations have not been reported between ionic and nonionic GBCA formulations¹⁴; however, nonionic agents tend to have lower osmolality and are less viscous,¹⁵ important traits under certain circumstances (i.e., use of power injectors).¹⁵ Low-viscosity GBCAs require less pressure to inject and can be administered using smaller gauge needles or catheters. Using low-viscosity agents with lower pressure levels makes rapid injection rates better tolerated.¹⁶ Nonionic low-osmolar GBCAs also cause fewer negative inotropic effects, an important consideration for cardiac patients.¹⁶ Ionic- and intermediate-osmolality GBCAs can lead to tissue necrosis following inadvertent extravasation,¹⁷ whereas nonionic GBCAs tend to be less toxic in this situation.¹⁶ Nonionic chelates have been reported to be less stable than ionic agents with respect to binding of the chelate to gadolinium. The nonionic formulation, especially the nonionic linear molecule, has a weaker binding to Gd^{3+} compared to the ionic agents.^{13,18}

TABLE 5. Administration of GBCAs

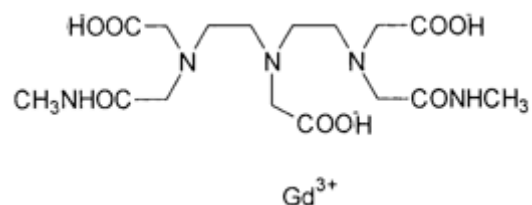
High-dose or bolus injection	Low osmolar nonionic GBCAs offer lower osmolar load ¹⁹
High-speed	Low viscosity agents reduce the risk of injector rupture and extravasation ²⁰
Routine	Low osmolar agents reduce the risk of extravasation, ²¹ and nonionic agents induce less inflammation and necrosis following an inadvertent extravasation ¹⁷

As mentioned earlier, for use in humans, gadolinium must be chelated to reduce its toxicity. From animal studies, chelated gadolinium has been shown to be 100-fold less toxic.¹¹ There are differences in the chemical structure of chelates used to bind the gadolinium ion (macrocyclic vs linear). The chemical structure of a typical linear and a typical macrocyclic GBCA are depicted in Figure 2.

The macrocyclic chelates tend to bind more tightly with gadolinium ions and in theory are more stable and have a lower dissociation rate than linear formulations, making them less likely to release free gadolinium, which can cause a toxic reaction.¹³ Most approved MRI agents in the United States are linear (six linear, one macrocyclic [Gadoteridol]). Although the approved macrocyclic GBCA is more stable than the approved linear compounds, all macrocyclic formulations are not necessarily more stable than their linear analogs; macrocyclic formulations have been described that are less stable than their linear analogs.⁹



2A. Typical macrocyclic agent (Gadobutrol)



2B. Typical linear agent (Gadodiamide)

FIGURE 2. Chemical Structures of GBCAs

ADVERSE REACTIONS

Mild adverse reactions such as nausea or hives occasionally occur following GBCA administration.¹⁵ Other uncommon adverse events include headache, taste disturbance, dizziness, and paraesthesia.²² Anaphylactoid reactions have been reported, but they are very infrequent.¹⁵ While adverse reactions are rare in the general patient population, they are more common in patients with a history of asthma or allergy, and in patients injected at a faster rate.¹⁰ These types of adverse events are similar with all GBCAs, with no significant differences between agents.^{10,15}

Early investigations reported that relative to iodinated contrast agents used in x-ray procedures, GBCAs are not nephrotoxic, giving them a significant advantage in patients with renal insufficiency.²³ However, increased off-label use of GBCAs at high doses (i.e., CT angiography and digital subtraction angiography) has increased safety concerns, especially in patients with chronic renal insufficiency.^{10,11} Based on this recent nephrotoxic data, the European Society of Urogenital Radiology and several authors have recommended that GBCAs should not be used in place of iodinated CM in patients with CKD or renal insufficiency.^{10,11}

Although no data has been reported on the safety of these agents in the pediatric population or during pregnancy, no GBCAs are approved for use during pregnancy^{10,22} or in children less than two years old.

EXTRAVASATION

Extravasation is the accidental release of medicinal drugs into the surrounding tissue during vascular administration. Monitoring a patient for extravasation can be

a challenge in MRI, especially when the patient is deep in the bore of the MR unit, some distance from the clinician. An extravasation can occur at a distance from the injection site.¹⁶ Extravasation of GBCAs into surrounding tissues can cause edema, inflammation, and necrosis¹⁰; however, in most cases the effect is minimal with no long-term sequelae. Certain patients, however, are less able to tolerate extravasation. These include²¹:

- Infants and young children
- Unconscious and debilitated patients
- Patients receiving chemotherapy
- Patients with arterial insufficiency
- Compromised venous or lymphatic drainage

As mentioned earlier, low-osmolar nonionic GBCAs reduce the risk of an extravasation because they tend to be lower viscosity, and because they are better tolerated, they reduce the severity following an occurrence.²¹

NEPHROGENIC SYSTEMIC FIBROSIS

The risk of nephrogenic systemic fibrosis (NSF) has become a big issue in radiology. It was first observed by Cowper et al in 1997 and published in 2000.²⁴ Initially called nephrogenic fibrosing dermopathy because the cutaneous changes consisted largely of indurated plaques and papules on the extremities and trunk in patients with renal disease,²⁵ NSF was recognized as a severely disabling systemic fibrosing condition resulting in increased morbidity and mortality. They had no idea what caused this condition, and they speculated that it was caused by an infectious and/or toxic agent. It wasn't until 2006 that the association of NSF with GBCAs was first described by Grobner.²⁶ Many other contributing factors for NSF have also been reported, including hypercoagulation syndromes, elevated parathyroid hormone, hypothyroidism, antiphospholipid antibodies, deep vein thrombosis, metabolic acidosis, high dose erythropoietin administration, and surgical or vascular interventions. Although the cause of NSF remains speculative, retrospective studies have suggested that exposure to a GBCA alone is not responsible for NSF and that other risk factors seem necessary for the development of NSF in the majority of cases.^{27,28} A cumulative risk factor model of NSF has been proposed (Figure 3) that may help to explain the diversity of NSF patients. This model proposes that patients with higher cumulative risk are more vulnerable to NSF and may need only low dosages of GBCA to trigger the development of NSF.²⁸

The number of reported NSF cases varies greatly depending on who is doing the reporting, and there are quite a few organizations that collect data on NSF (i.e., manufacturers, FDA MedWatch, European Pharmacovigilance Working Party, and the NSF

Registry). The NSF Registry has identified over 335 cases.²⁹ However, according to an FDA briefing document using data provided by companies that manufacture GBCAs, there have been 1,161 reported cases of NSF globally.³⁰ According to FDA documents, the reliability of this data is limited by the "variable definition of a reported case, the lack of consistent criterion until 2009 for the diagnosis of NSF, an undetermined number of duplicate reports, a lack of dosing information, and lack of information concerning renal function testing." In any case, the number of reported cases indicates that NSF is a very rare event, especially when you consider that in the United States, 30% of the 31 million annual MR examinations are performed using GBCAs to enhance the image,³¹ and the total number of patients who received GBCA is estimated to be over 200 million globally.³²

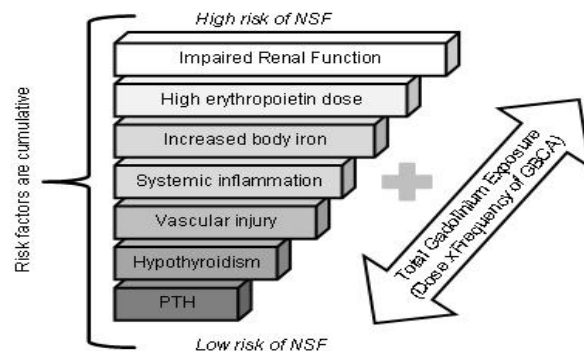


FIGURE 3. Cumulative Risk Factor Model of NSF Showing Inverse Relationship between Gadolinium Dosage and Extent of Risk Factors for NSF²⁸

Adapted from Swaminathan S, Shah MV. New insights into nephrogenic systemic fibrosis. *J Am Soc Nephrol.* 2007;18:2636-43.

Although this condition is extraordinarily rare, in patients with markedly reduced kidney function, the incidence is substantially higher, ranging from 2.9% to 4.0%.²⁴ NSF is known to occur exclusively in patients with decreased renal function (glomerular filtration rate < 30mL/min/1.73m²).^{11,33} The current theory on the etiology of NSF proposes that because of the prolonged clearance time of GBCAs in renally-impaired patients,¹¹ gadolinium chelates have a propensity to undergo transmetalation, in which other cations in the body displace gadolinium from its chelate,¹¹ releasing free gadolinium which is then deposited in various tissues. This syndrome can include fibrosis of skeletal muscle, lungs, testes, and myocardium that can be debilitating, and in some cases fatal.²⁸ However, this theory is based on differences in the thermodynamic stability constants of these agents and there is no clinical evidence to support this hypothesis. The pathogenesis of NSF is not yet established.

NSF cases have been reported for all GBCAs.

Although the majority of NSF cases involve the linear GBCAs—the most commonly reported agent was gadodiamide followed by gadopentetate and gadoversetamide³³—NSF has also been reported for gadoteridol, the macrocyclic formulation.³³⁻³⁵ In spite of these differences in the incidence of NSF, there is no evidence that any of the approved GBCAs are safe in the at-risk patient population (eGFR < 30mL/min/1.73m²).³⁶ Conversely, in patients without renal disease, all gadolinium-based contrast agents seem to be safe.³²

There are still a lot of unanswered questions about NSF. For example, only a small proportion of severe renally-impaired patients that receive GBCAs actually develop NSF. Most don't. Some at-risk patients develop NSF, and others don't. And then there are those reports of NSF in patients with no history of exposure to GBCAs.^{13,37}

Regarding the relative safety of the various GBCAs, the American College of Radiology (ACR) Manual on Contrast Media states, "It must be emphasized that the frequency with which NSF has been associated with different GBCM may reflect a combination of differences in agent toxicity and market share. In addition, reported frequency is also further confounded by the fact that some agents, particularly gadodiamide, may have been used disproportionately more frequently in patients receiving high doses of GBCM for magnetic resonance angiography."³⁶ It should be noted, however, that gadodiamide is not approved for magnetic resonance angiography.

Similarly, the FDA, recognizing that it is not possible to know if the extent of risks for developing NSF is the same for all agents and suggesting that all gadolinium chelates are potentially linked to NSF, has asked all manufacturers to include a boxed warning on the product labeling of all GBCAs used to enhance MRI (Figure 4).³³

It is clear that in the vast majority of cases, nephrogenic systemic fibrosis has been reported only in patients with acute or chronic severe renal insufficiency (eGFR < 30mL/min/1.73m²), and there have been no reports of NSF in patients with normal kidney function.³²

GUIDELINES ON GBCA USAGE

The FDA does not state that any specific preparation is contraindicated; however, it does recommend that physicians carefully consider the need for any gadolinium chelate in patients with increased risk for NSF (i.e., patients with acute or chronic severe renal insufficiency [GFR < 30mL/min/1.73m²]) or acute renal insufficiency due to hepatorenal syndrome or in the perioperative liver transplant period.^{11,33}

The ACR recommends that, prior to an MRI using a GBCA, physicians should identify patients who have severe renal failure (GFR < 30mL/min/1.73m²) by questioning patients for a history of renal disease and should obtain an eGFR measurement within six weeks

of the procedure in patients with renal disease (including patients with a solitary kidney, renal transplant, or renal neoplasm), in anyone over 60 years old, or in patients with hypertension, diabetes mellitus, or a history of severe liver disease.³⁶ When a high-risk patient is identified, the ACR recommends considering alternative studies and informing these patients about the potential risks of GBCA-enhanced studies, should such studies be deemed necessary, using the lowest possible dose of GBCA to obtain the necessary clinical information, and avoiding double or triple dose studies, if possible, and avoiding using those GBCAs that have been most frequently associated with NSF.

The ACR has specific recommendations for high-risk groups based on kidney function (Figure 5).

CKD STAGE 4 OR 5

This patient group is problematic because an iodinated CM can worsen renal function requiring dialysis, and a GBCA for MRI could lead to NSF. Data suggests that patients with eGFR < 15 mL/min/1.73m² (stage V CKD) have the greatest risk of NSF. In these patients, it is recommended that any contrast media administration be avoided if at all possible. If an MRI is absolutely essential, the physician should use the lowest possible dose and, although there is no proof that any GBCA is completely safe in this patient group, some have suggested avoiding gadodiamide and considering the use of a macrocyclic agent.³⁶

CKD STAGE 3

For patients with eGFR between 30-59mL/min/1.73m² (stage III CKD), there is an extremely low, or no, risk for NSF using a GBCA dose of ≤0.1 mmol/kg.³⁶

CKD STAGE 1 OR 2

There is no evidence of increased risk of NSF in patients with eGFR 60-119 mL/min/1.73m² (stage I or II CKD). All GBCAs can be safely administered using a dose of ≤ 0.1 mmol/kg.³⁶

IDENTIFYING AND MANAGING THE AT-RISK PATIENT

Chronic kidney disease is often asymptomatic and may be undetected prior to GBCA-enhanced MRI. The National Health and Nutrition Examination Survey (NHANES) examined the prevalence of CKD in the United States from 1999-2004 among adults 20 years or older, and they reported that 5.7% of this population had Stage I CKD, 5.4% had Stage II, 5.4% had Stage III, and 0.4% had Stage IV-V.³⁹ From this data, only 0.4% of the adult United States population is at risk for NSF (Figure 6).

Boxed Warning:

- Exposure to GBCAs increases the risk for NSF in patients with:
 - acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²), or
 - acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
- Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- When administering a GBCA, do not exceed the dose recommended in product labeling. Allow sufficient time for elimination of the GBCA prior to any readministration.

FIGURE 4. GBCA Boxed Warning³³

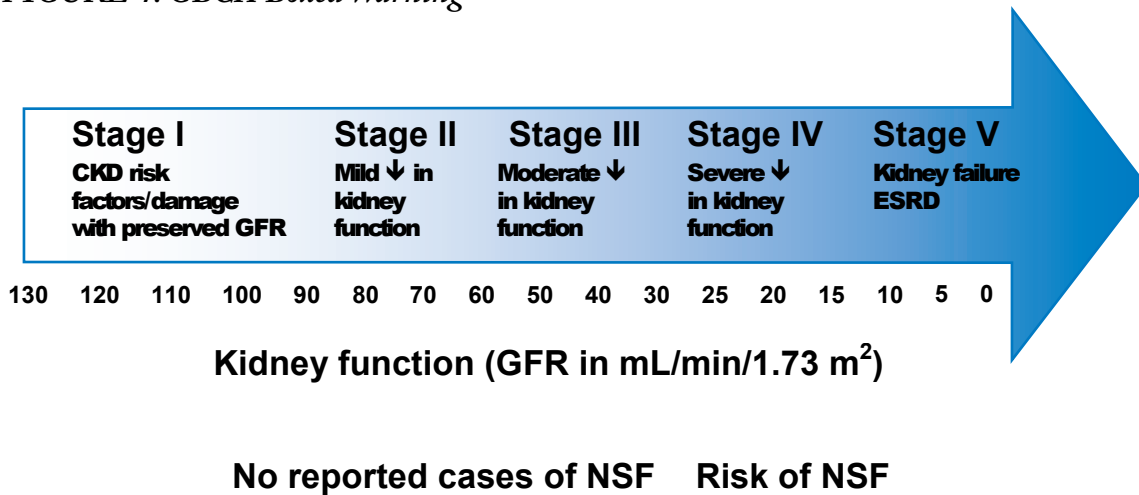


FIGURE 5. Stages of Chronic Kidney Disease (CKD)³⁸

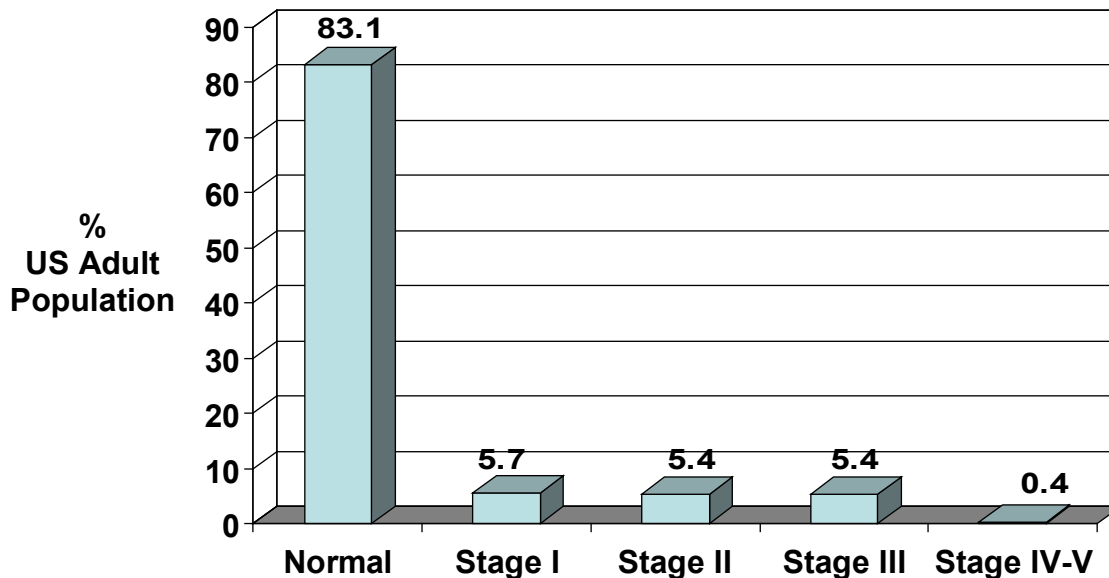


FIGURE 6. Prevalence of CKD in the United States from 1999-2004 in Adults 20 Years or Older³⁹

Because it is clear that chronic kidney disease is associated with the risk of NSF, most guidelines recommend that physicians assess renal function prior to a GBCA-enhanced MRI procedure to determine baseline renal function. Renal function can be estimated using specially derived predictive equations based on serum creatinine (SCr) measurements.

Because these tests can be uncomfortable, time consuming, and expensive, a patient questionnaire has been developed to identify patients at risk of having abnormal renal function.⁴⁰ The six questions most strongly associated with elevated SCr are as follows:

1. Have you ever been told you have renal problems?
2. Have you ever been told you have protein in your urine?
3. Do you have high blood pressure?
4. Do you have diabetes?
5. Do you have gout?
6. Have you ever had kidney surgery?

If the answer to any of these questions is “yes,” it is recommended that a SCr measurement be taken to calculate the patient’s eGFR before a GBCA is administered.¹³ Using this questionnaire, in 67% of the patients who responded “no” to all six of these questions, there was a high likelihood that their SCr level would be normal (94%). Although this survey was designed to identify patients with kidney disease and other risk factors for contrast-induced nephropathy prior to administering an iodinated contrast agent, it could also help to identify patients at higher risk for NSF.

As healthcare providers have been restricting their use of GBCAs in patients at risk for NSF, the incidence of NSF in the United States has been dropping. This reduction reflects the changes that have been implemented in radiology practice since the risks of NSF have been widely publicized.⁴¹

CONCLUSION

GBCA-enhanced MRI has proven to be an invaluable diagnostic tool distinguished not only by its ability to provide a high level of contrast between tissues, but also by the range of anatomical and physiological information it provides. Millions of doses of GBCAs have been administered annually to enhance the clinical usefulness of MR images.

The link between GBCAs and the risk of NSF has greatly affected radiology departments. Although the incidence of NSF is extraordinarily low in patients with normal kidney function, in at-risk, renally-impaired patients, the incidence is higher (approximately 2.9% to 4.0%). The extensive attention paid to GBCAs,

NSF, and the FDA’s boxed warning has greatly reduced the incidence of GBCA-related NSF. Although a cause-and-effect relationship between GBCAs and NSF has not been established, it is clear that NSF occurs exclusively in patients with severe to end-stage CKD (eGFR < 30 mL/min/1.73m²), and exposure to all GBCAs in this patient population should be avoided if at all possible.

Hopefully, by observing the new guidelines and protocols, radiologists can now continue to generate high quality GBCA-enhanced MR images while protecting their patients from NSF.

REFERENCES

1. Strijkers GJ, Mulder WJ, van Tilborg GA, Nicolay K. MRI contrast agents: current status and future perspectives. *Anticancer Agents Med Chem.* 2007;7:291-305.
2. Sands MJ, Levitin A. Basics of magnetic resonance imaging. *Semin Vasc Surg.* 2004;17:66-82.
3. Damadian R, Goldsmith M, Minkoff L. NMR in cancer: XVI. FONAR image of the live human body. *Physiol Chem Phys.* 1977;9:97-100.
4. The Royal College of Ophthalmologists MRI Scans T1 and T2. Available at: <http://www.mrcophth.com/mriscan/t1andt2.html>. Accessed 4/5/2010.
5. Baur L. Imaging Cardiac Tumors. CEWebsitesource.com Website [serial online]. Available at: <http://www.cewebsitesource.com/coursePDFs/cardiactumors.pdf>. Accessed April 4, 2010.
6. Luse K. Taking MRI to Heart. CEWebsitesource.com Website [serial online]. Available at: <http://www.cewebsitesource.com/coursePDFs/takingMRI2Heart.pdf>. Accessed April 4, 2010.
7. Trovinger A. Diffusion and Perfusion MRI in Acute Stroke Imaging. CEWebsitesource.com Website [serial online]. Available at: <http://www.cewebsitesource.com/coursePDFs/diffusionPerfusionMRI.pdf>. Accessed April 4, 2010.
8. Kirby MW, Spritzer C. Radiographic detection of hip and pelvic fractures in the emergency department. *Am J Roentgenol.* 2010;194:1054-60.
9. Sherry AD, Caravan P, Lenkinski RE. Primer on gadolinium chemistry. *J Magn Reson Imaging.* 2009;30:1240-8.
10. Ersoy H, Rybicki FJ. Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. *J Magn Reson Imaging.* 2007;26:1190-7.
11. Penfield JG, Reilly RF Jr. What nephrologists need to know about gadolinium. *Nat Clin Pract Nephrol.* 2007;3:654-68.
12. U.S. Food and Drug Administration: Advisory Committees, December 8, 2009: Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting Announcement. Available at: <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm186142.htm>. Accessed April 13/2010.
13. Kei PL, Chan LP. Gadolinium chelate-associated nephrogenic systemic fibrosis. *Singapore Med J.* 2008;49:181-5.
14. Knopp MV, von Tengg-Kobligh H, Floemer F, Schoenberg SO. Contrast agents for MRA: future directions. *J Magn Reson Imaging.* 1999;10:314-6.

15. Muroff LR. MRI contrast: current agents and issues. *Appl Radiol.* 2001;30(suppl):5-7.
16. Tanenbaum LN. MR contrast agents: advanced power-injected applications. *Appl Radiol.* 2001;30(suppl):20-25.
17. Runge VM, Muroff LR, Jinkins JR. Central nervous system: review of clinical use of contrast media. *Top Magn Reson Imaging.* 2001;12:231-63.
18. Morcos SK. Chronic kidney disease: CT or MRI? *Appl Radiol.* 2008;37:19-24.
19. Colosimo C, Manfredi R, Tartaglione T. Contrast enhancement issues in the MR evaluation of the central nervous system. *Eur Radiol.* 1997;7 (suppl 5):231-7.
20. U.S. Food and Drug Administration. Center for Devices and Radiological Health. Reminders from FDA regarding ruptured vascular access devices from power injection. Available at: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm070193.htm>. Accessed April 26, 2010.
21. Bellin MF, Jakobsen JA, Tomassin I, et al. Contrast medium extravasation injury: guidelines for prevention and management. *Eur Radiol.* 2002;12:2807-12.
22. Kalva SP, Blake MA, Sahani DV. MR contrast agents. *Appl Radiol.* 2006;35:18-27.
23. Maki JH, Chenevert TL, Prince MR. Contrast-enhanced MR angiography. *Appl Radiol.* 2003;3(suppl):5-20.
24. Cowper SE. Gadolinium – is it to blame? *J Cutan Pathol.* 2008;35:520-2.
25. Cowper SE, Su LD, Bhawan J, Robin HS, LeBoit PE. Nephrogenic fibrosing dermopathy. *Am J Dermatopathol.* 2001;23:383-93.
26. Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant.* 2006;21:1104-8.
27. Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. *Clin J Am Soc Nephrol.* 2007;2:264-7.
28. Swaminathan S, Shah MV. New insights into nephrogenic systemic fibrosis. *J Am Soc Nephrol.* 2007;18:2636-43.
29. Cowper SE. Nephrogenic Fibrosing Dermopathy [ICNSFR Website]. 2001-2009. Available at: <http://www.icnsfr.org>. Accessed April 5, 2010.
30. Forrest W. FDA meeting to review NSF and gadolinium MRI contrast link. November 24, 2009. AuntMinnie.com Website. Available at: <http://www.auntminnie.com/index.asp?Sec=sup&Sub=mri&Pag=dis&ItemId=88407>. Accessed April 16, 2010.
31. Colletti PM. Nephrogenic systemic fibrosis and gadolinium: a perfect storm. *AJR.* 2008;191:1150-3.
32. Thomsen HS. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. *Eur Radiol.* 2006;16:2619-21.
33. U.S. Food and Drug Administration Alert: Information for healthcare professionals: Gadolinium-based contrast agents for magnetic resonance imaging, 5/23/2007. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142884.htm>. Accessed October 30, 2008.
34. Elmholdt TR, Jorgensen B, Ramsing M, Pedersen M, Olesen AB. Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gabobutrol. NDT Plus Advance Access. Published online on March 19, 2010. Available at: <http://ndtplus.oxfordjournals.org/cgi/content/abstract/sfq028>. Accessed April 12, 2010.
35. ProHance/ProHance Multipack. Advisory Committee Briefing Document Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Gadolinium Based Contrast Agents. NDAs 200-131/21-489. Submitted by Bracco October 30, 2009.
36. American College of Radiology. Manual on Contrast Media. Version 6. 2008. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx. Accessed October 30, 2008.
37. Cheng S, Abramova L, Saab G, et al; Centers for Disease Control and Prevention. Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents—St Louis, Missouri, 2002-2006. *MMWR.* 2007;56:137-41.
38. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Executive Summary. *Am J Kidney Dis.* 2004;43(5 suppl 1):S16-S41.
39. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis.* 2003;41:1-12.
40. Choyke PL, Cady J, DePollar SL, Austin H. Determination of serum creatinine prior to iodinated contrast media: is it necessary in all patients? *Tech Urol.* 1998;4:65-9.
41. Forrest W. FDA panel: NSF incidence falls with gadolinium restrictions. December 9, 2009. AuntMinnie.com Website. Available at: <http://www.auntminnie.com/index.asp?Sec=sup&Sub=mri&Pag=dis&ItemId=88744>. Accessed April 16, 2010.

REVIEW OF GBCAs IN MRI POST TEST

Expires: August 15, 2012 Approved for 1 ARRT Category A Credit.

1. **Magnetic resonance imaging (MRI) employs**
 - a. ionizing radiation.
 - b. a magnetic field.
 - c. a radio frequency pulse.
 - d. both b and c.
2. **Unlike CT scans, MRI uses**
 - a. no ionizing radiation.
 - b. no iodinated contrast agents.
 - c. nephrotoxic contrast agents.
 - d. both a and b.
3. **The basis of MRI images involves which atom?**
 - a. Oxygen
 - b. Carbon
 - c. Hydrogen
 - d. Nitrogen

4. **Which of the following contrast agents is most often used to enhance MRIs?**
 - a. Gadolinium-based contrast agents
 - b. Iodinated contrast media
 - c. Water
 - d. Barium
5. **What is the term used to describe the rotation of hydrogen atoms in a magnetic field?**
 - a. Excitation
 - b. Relaxation
 - c. Precession
 - d. Polarization
6. **T1-weighted images refers to**
 - a. relaxation in the longitudinal magnetic field.
 - b. relaxation in the transverse magnetic field.
 - c. relaxation in all magnetic fields.
 - d. both a and b.
7. **Water in a T1-weighted image will appear**
 - a. light gray.
 - b. black.
 - c. clear.
 - d. white.
8. **MRI has recently been shown to be superior to radiographic images in which of the following?**
 - a. Stroke
 - b. Acute MI
 - c. Bone fractures
 - d. Chest pain
9. **Free gadolinium is most toxic because it competes with which of the following?**
 - a. Magnesium
 - b. Calcium
 - c. Iron
 - d. Potassium
10. **Binding or chelating free gadolinium to an organic ligand makes it**
 - a. less toxic.
 - b. more water soluble.
 - c. easier to excrete.
 - d. both a and b.
11. **Currently, there are how many approved GBCAs in the United States?**
 - a. 9
 - b. 8
 - c. 7
 - d. 6
12. **Gadolinium-based contrast agents can be characterized by their**
 - a. binding to protein.
 - b. ionic charge (ionic vs nonionic).
 - c. magnetic charge.
 - d. both a and b.
13. **Almost all GBCAs are**
 - a. excreted in the urine.
 - b. excreted in the feces.
 - c. not metabolized before being excreted.
 - d. both a and c.
14. **Low-viscosity GBCAs are**
 - a. usually nonionic and low osmolar formulations.
 - b. usually ionic and high osmolar formulations.
 - c. excreted in the feces.
 - d. always more difficult to inject.
15. **Which GBCAs tend to be more stable?**
 - a. Nonionic formulations
 - b. Macrocyclic molecular structure
 - c. Ionic formulations
 - d. Both a and b
16. **Which GBCAs have the most serious adverse reactions?**
 - a. Ionic
 - b. Nonionic
 - c. Linear
 - d. Most GBCAs are similar with respect to adverse reactions.
17. **Extravasation of a GBCA can cause**
 - a. edema.
 - b. nose bleeds.
 - c. necrosis.
 - d. both a and c.
18. **The most serious risk of GBCAs is**
 - a. extravasation.
 - b. nephrogenic systemic fibrosis.
 - c. adverse reaction.
 - d. allergic reaction.
19. **Nephrogenic systemic fibrosis has been reported only in patients with**
 - a. normal kidney function.
 - b. diabetes.
 - c. serious decreased renal function.
 - d. high blood pressure.
20. **Prior to an MRI procedure, physicians should identify patients at risk of NSF, who have which stage of chronic kidney disease?**
 - a. Stage I
 - b. Stage II
 - c. Stage III
 - d. Stage IV–V

