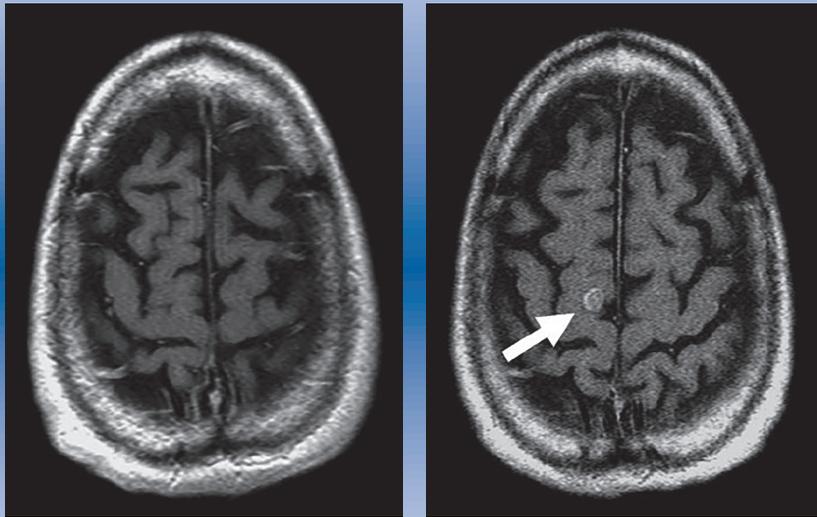


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THE JOURNAL OF PRACTICAL MEDICAL IMAGING AND MANAGEMENT



## Considerations in the Selection of a New Gadolinium-Based Contrast Agent

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# Considerations in the Selection of a New Gadolinium-Based Contrast Agent

Our 3 esteemed faculty summarize the similarities and differences among the gadolinium-based contrast agents (GBCAs) currently utilized for magnetic resonance imaging (MRI), with emphasis on stability and relaxivity. Dr. Michael Tweedle focuses on the chemical design and properties of the macrocyclic GBCAs and Dr. Robert Muller focuses on the molecular structures of the linear agents, and how the ability to interact with serum proteins contributes to differences in relaxivity among these agents. Dr. Emanuel Kanal provides a clinical perspective, reviewing how both stability and relaxivity impact efficacy and safety. The goal of this supplement is to help radiologic technologists expand their understanding of the physicochemical properties of the various available GBCAs in order to better select among them for various applications.



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# CE Accreditation Information

## Considerations in the Selection of a New Gadolinium-Based Contrast Agent

### Program Information

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### Faculty

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Robert Muller, PhD, University of Mons

### Target Audience

Radiologic Technologists

### Learning Objectives

Upon completion, participants should:

- Understand the physicochemical similarities and differences among the available GBCAs
- Understand how the chemical design of each agent affects its relaxivity
- Understand the important practical issues of stability and safety

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# Considerations in the Selection of a New Gadolinium-Based Contrast Agent

Michael F. Tweedle, PhD, Emanuel Kanal, MD, FACR, FISMRM, and Robert Muller, PhD

The use of gadolinium-based contrast agents (GBCAs) to enhance the sensitivity and specificity of magnetic resonance imaging (MRI) has been part of standard clinical practice for over 2 decades. Currently, there are 9 GBCAs approved by the U.S. Food and Drug Administration (FDA) that vary in a number of properties, some of which may significantly impact their clinical utility, particularly for specific applications. So what criteria should radiologists use to select a GBCA? Of the various physicochemical properties, the criteria most important to radiologists for optimization of diagnostic efficacy and patient safety are relaxivity and stability.

A GBCA with a higher relaxivity provides increased signal intensity, greater contrast enhancement, and improved diagnostic efficacy.<sup>1-3</sup> In addition, the higher signal seen with higher-relaxivity agents affords the potential to use lower doses in patients at risk of developing nephrogenic systemic fibrosis (NSF).<sup>4-9</sup> Stability is an important consideration

because free gadolinium ( $Gd^{3+}$ ) is toxic and, therefore, the ability of the ligand to bind tightly to the Gd ion is an important safety consideration.<sup>10</sup> Moreover, since 2006, when an association was made between the development of NSF and the administration of Gd,<sup>11</sup> stability has become an even greater concern in the selection of a GBCA.

The 9 available GBCAs can be classified on the basis of relaxivity into 3 groups: macrocyclic standard relaxivity agents (including gadoterate meglumine [Dotarem],<sup>12</sup> gadobutrol [Gadavist],<sup>13</sup> and gadoteridol [ProHance]),<sup>14</sup> linear standard relaxivity agents (gadopentate dimeglumine [Magnevist]),<sup>15</sup> gadodiamide [Omniscan],<sup>16</sup> and gadoversetamide [OptiMARK]),<sup>17</sup> and high-relaxivity agents, which interact with or overtly bind to proteins (the blood pool agent gadofosveset trisodium [Ablavar],<sup>18</sup> the liver imaging agent gadoxetic acid [Eovist],<sup>19</sup> and the multipurpose agent gadobenate dimeglumine [MultiHance]<sup>20</sup> (Table 1). While all 3 of these high-relaxivity agents are linear in structure, there are some interesting observations regarding unconfounded NSF association – or lack thereof – with these agents that will be covered below.

Here we describe the differences among these 3 groups of GBCAs, including the advantages and disadvantages of their physicochemical profiles as they pertain to the selection of a GBCA. In addition, we summarize the pub-

lished evidence surrounding the efficacy and safety of these 3 groups of agents. Finally, we discuss considerations when adopting a new GBCA for a radiology practice in order to maximize diagnostic yield while minimizing patient risk.

## Macrocyclic GBCAs

Three macrocyclic agents are currently approved by the FDA: gadoterate meglumine (Dotarem), gadobutrol (Gadavist), and gadoteridol (ProHance). In terms of relaxivity, all are nonprotein binding and, therefore, standard relaxivity, with  $r1$  relaxivities in the range of 4 to 5  $L \cdot mmol^{-1} \cdot s^{-1}$ .<sup>21</sup> In terms of stability, macrocyclic agents utilize a closed, cage-like ligand that surrounds and binds tightly to the Gd ion, resulting in highly stable complexes (Table 2).<sup>10</sup> Many published studies exist to support the high stability of these macrocyclic agents relative to the linear agents and, in terms of clinical value, these data can be considered to exist within a hierarchy, from in vitro, test-tube data at the bottom all the way up to human in vivo data at the top (Figure 1). When assessing the various data, it is important to recognize that higher-level data (eg, clinical experience) always trump data lower on the hierarchy (eg, test tube numbers).

Test-tube data derived from GBCAs in solution demonstrate that as a class, the macrocyclic agents have high thermodynamic binding constants ( $\log K_{therm}$

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**Table 1. Currently available GBCAs.<sup>12-20,41</sup>**

	Chemical Name	Trade Name	Structure	Ionicity	Concentration (M)	Clinical Use
Standard relaxivity	Gadoterate meglumine	Dotarem	Macrocyclic	Ionic	0.5	Multipurpose
	Gadobutrol	Gadavist	Macrocyclic	Nonionic	1.0	Multipurpose
	Gadoteridol	ProHance	Macrocyclic	Nonionic	0.5	Multipurpose
	Gadopentetate dimeglumine	Magnevist	Linear	Ionic	0.5	Multipurpose
	Gadoversetamide	OptiMARK	Linear	Nonionic	0.5	Multipurpose
	Gadodiamide	Omniscan	Linear	Nonionic	0.5	Multipurpose
High relaxivity, protein interacting	Gadofosveset trisodium	Ablavar	Linear	Ionic	0.25	Blood Pool
	Gadoxetic acid	Eovist	Linear	Ionic	0.25	Liver
	Gadobenate dimeglumine	MultiHance	Linear	Ionic	0.5	Multipurpose

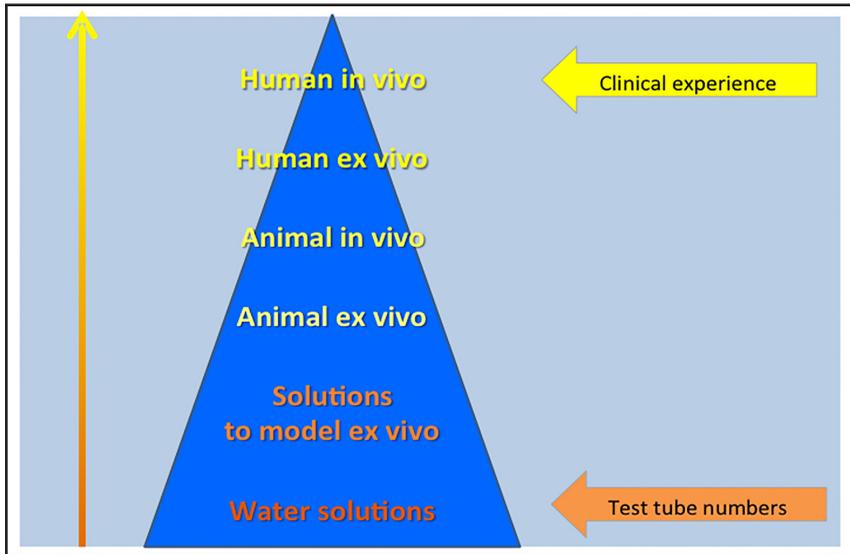
and log  $K_{cond}$  [essentially log  $K_{therm}$  measured at physiologic pH]) (Table 2).<sup>10</sup> In vivo, the dissociation of GBCAs into gadolinium ion and ligand can be facilitated by a number of competing endogenous metals, such as zinc, copper, calcium, and iron, all of which may work simultaneously to destabilize the complex and lead to its dissociation. This displacement of the gadolinium ion from its ligand by other metals through competitive ionic binding is termed transmetallation (or dissociation or dechelation), and transmetallation has been studied both in vivo and in vitro. In vitro, copper and zinc ion stress test data demonstrate that in the presence of these competitors, the macrocyclic agents gadoterate meglumine (Dotarem) and gadoteridol (ProHance) remain essentially intact (<1% reaction), while the less stable linear agents gadodiamide (Omniscan) and gadopentetate dimeglumine (Magnevist) are more highly reactive.<sup>22</sup> In vivo data from mice and rats also demonstrate that up to 14 days after injection of radiolabeled GBCAs, the lowest levels of residual Gd are observed with the macrocyclic agents<sup>23</sup> (Figure 2).

**Table 2. Thermodynamic constants of GBCAs.<sup>13</sup>**

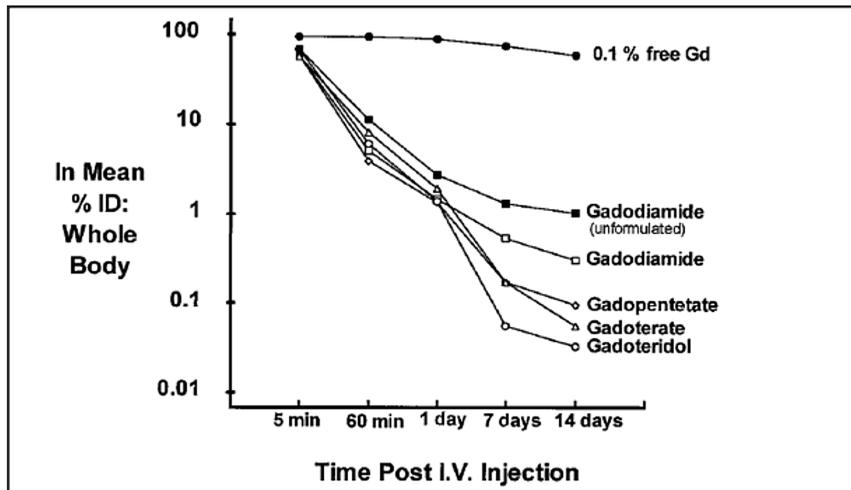
Chemical Name	Trade Name	log $K_{therm}$	log $K_{cond}$
Gadoterate meglumine	Dotarem	25.6	19.3
Gadobutrol	Gadavist	21.8	14.7
Gadoteridol	ProHance	23.8	17.1
Gadopentetate dimeglumine	Magnevist	22.1	17.7
Gadoversetamide	OptiMARK	16.6	15.0
Gadodiamide	Omniscan	16.9	14.9
Gadofosveset trisodium	Ablavar	22.1	18.9
Gadoxetic acid	Eovist	23.5	18.7
Gadobenate dimeglumine	MultiHance	22.6	18.4

Human ex vivo data also demonstrate that transmetallation can occur with the low stability, linear agents gadodiamide (Omniscan) and gadoversetamide (OptiMARK). In this case, the data come from the observation that these 2 agents (and not the more stable agents) interfere in the

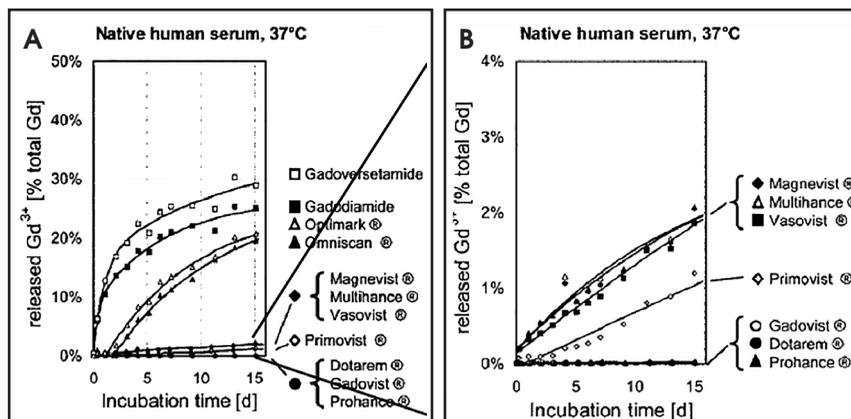
colorimetric serum assay for calcium.<sup>24</sup> The mechanism for this interference is believed to be removal of the Gd from the ligand-Gd complex by the specific dye used in the assay, preventing the dye from binding calcium.<sup>24</sup> The result is a spurious hypocalcemia result for the patient, with potentially harmful



**FIGURE 1.** Hierarchy of data: from solutions in a test tube to human in vivo data.



**FIGURE 2.** Residual <sup>153</sup>Gd in mice as a percent of the injected dose (% ID) after intravenous administration of Gd chelates.<sup>23</sup>



**FIGURE 3.** Amounts of gadolinium ions released from 1 mM solutions of (A) all marketed GBCAs at 37°C in native human serum from healthy volunteers; (B) a section of the graph has been enlarged to permit better visualization of data for the ionic linear and macrocyclic GBCAs.<sup>25</sup>

clinical consequences. More recently, it was demonstrated that up to 20% of the nonionic linear GBCAs dissociate in human plasma up to 2 weeks after administration, while for the ionic linear agents and the macrocyclics, that number was closer to 2% and 0%, respectively (Figure 3).<sup>25</sup> Human in vivo data, the most credible data, also exist to support the high stability of the macrocyclic agents: White and colleagues demonstrated 4 times more Gd<sup>3+</sup> deposited in the bone of hip replacement patients after administration of gadodiamide (Omniscan) vs gadoteridol (ProHance).<sup>26</sup>

Taken together, all of these data suggest that transmetallation occurs both ex vivo and in vivo, and that with low stability linear GBCAs, there is more marked displacement of the gadolinium ion from its ligand by other metals. It is notable that the only GBCA with a triple dose indication is one of the macrocyclic agents, gadoteridol (ProHance)<sup>14</sup> (the approval for triple dose indication for the linear agent gadodiamide [Omniscan] was withdrawn by the FDA in December, 2010).

It should also be noted that Pietsch and colleagues recently used a sensitive in vivo animal model to derive elimination time-courses for Gd in the skin of rats and found significantly higher nmolGd/g of skin at both Day 35 and Day 364 for the less stable agents compared with the macrocyclic agents (Table 3).<sup>27</sup> However, a very small amount of Gd was still present in the skin of rats administered a macrocyclic agent on day 364, indicating that although the risk of dissociation with macrocyclic GBCAs is very low, this “low risk” is not equivalent to “no risk” and therefore, in patients at highest risk of NSF, it is still best to carefully assess the risk vs the benefit of injecting any GBCA.

### Standard- and High-Relaxivity Linear Agents

The linear agents can be divided into nonprotein binding, standard-relaxivity GBCAs and protein interacting/binding, high-

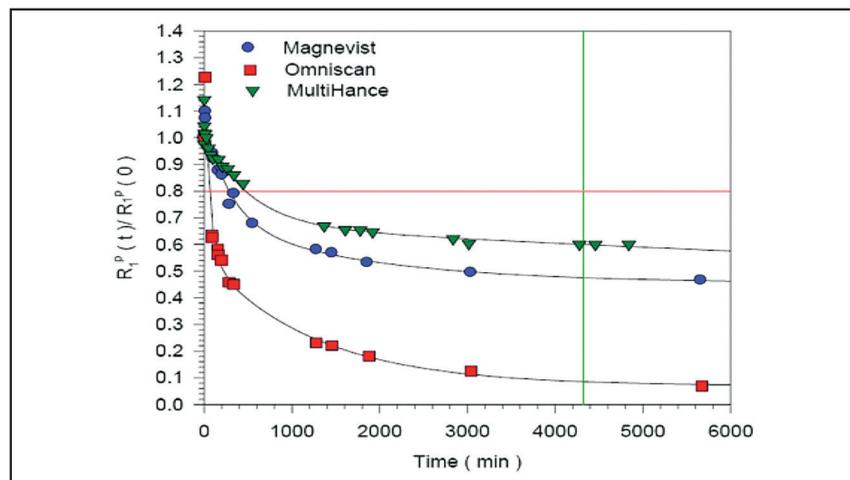
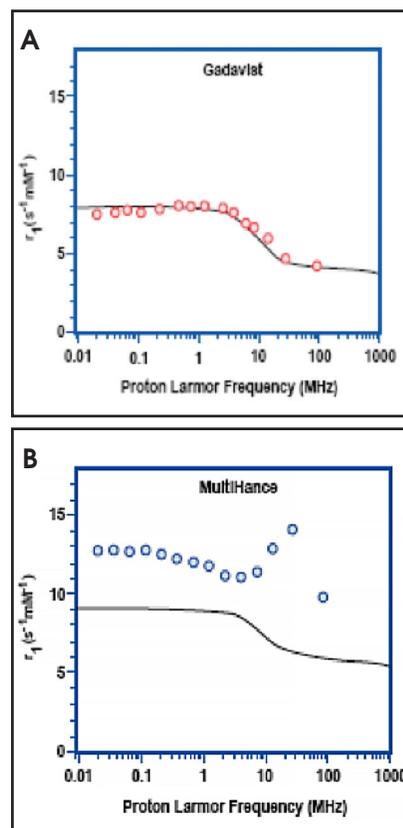
**Table 3. Concentration of Gd in skin biopsies taken from animals after treatment (injection with 2.5 mmol/kg per injection for 5 consecutive days) with various GBCAs.<sup>27</sup>**

Chemical Name	Trade Name	Concentration of gadolinium in skin	
		Day 35 Post-injection (nmolGd/g skin)	Day 364 Post-injection (nmolGd/g skin)
Gadodiamide	Omniscan	132 ± 23	72 ± 12
Gadoversetamide	OptiMARK	47 ± 5	18 ± 5
Gadopentetate dimeglumine	Magnevist	36 ± 6	9 ± 2
Gadobenate dimeglumine	MultiHance	7 ± 1	1.4 ± 0.4
Gadoterate meglumine	Dotarem	2 ± 1	0.22 ± 0.17
Gadobutrol	Gadavist	2 ± 1	0.06 ± 0.03
Gadoteridol	ProHance	2 ± 1	0.08 ± 0.02

**Table 4. r1 Relaxivities of linear GBCAs.<sup>21,39</sup>**

	Chemical Name	Trade Name	r1 relaxivity* (L·mmol <sup>-1</sup> ·s <sup>-1</sup> )
Standard relaxivity	Gadopentetate dimeglumine	Magnevist	3.9–4.1
	Gadoversetamide	OptiMARK	4.7
	Gadodiamide	Omniscan	4.3
High relaxivity, protein interacting	Gadofosveset trisodium	Ablavar	19
	Gadoxetic acid	Eovist	6.9
	Gadobenate dimeglumine	MultiHance	6.3–7.9

\*Measured at 1.5T in plasma at 37°C.


**FIGURE 4. More rapid and complete transmetallation by gadodiamide (Omniscan) over time compared with gadopentetate dimeglumine (Magnevist) and gadobenate dimeglumine (MultiHance).<sup>30</sup>**

**FIGURE 5. Apparent relaxivity profiles of solutions containing 1mM (A) gadobutrol (Gadavist) and (B) gadobenate dimeglumine (MultiHance) in the absence (lines) and presence (dots) of 4% human serum albumin.<sup>30</sup>**

relaxivity agents. Tables 2 and 4, respectively, show the stability and r1 relaxivity measurements for the various linear agents. The thermodynamic stability constant ( $K_{\text{therm}}$ ) is a measure of stability: a lower thermodynamic stability constant indicates that the  $\text{Gd}^{3+}$  ion will be more readily released.<sup>28</sup> However, the thermodynamic stability constant does not take pH into account. The conditional stability constant ( $K_{\text{cond}}$ ) is a measure of the stability of a complex at physiologic pH and, therefore,  $K_{\text{cond}}$  is considered a more relevant stability parameter. Note that the nonionic linear GBCAs gadodiamide (Omniscan) and gadoversetamide (OptiMARK) have the lowest conditional stability constants, and this low stability is believed to be related to the higher prevalence of NSF cases associated with these GBCAs.<sup>29</sup>

Based on in vitro Zn<sup>2+</sup> transmetallation data (Figure 4), gadodiamide (Omniscan) has lower stability and gadobenate dimeglumine (MultiHance) has higher stability compared with gadopentetate dimeglumine (Magnevist).<sup>30</sup> However, based on higher-level, human ex vivo data, there is essentially no difference in the amounts of Gd<sup>3+</sup> released among the ionic linear agents gadobenate dimeglumine (MultiHance), gadopentetate dimeglumine (Magnevist), and gadofosveset trisodium (Ablavar) when measured in native human serum at 37°C (Figure 3).<sup>25</sup>

How does protein interaction influence relaxivity? Interaction with serum proteins, most notably human serum albumin (HSA), greatly increases the effective size of the Gd-ligand complex, reducing its molecular

motion, leading to greater T1 shortening and substantially increased signal-intensity enhancement.<sup>31</sup> Gadofosveset trisodium (Ablavar), gadoxetate meglumine (Eovist), and gadobenate dimeglumine (MultiHance) all interact with HSA, the first strongly and the last 2 weakly.<sup>30</sup>

Figure 5 shows the relaxivity profiles of solutions containing 1mM of either gadobutrol (Gadavist) or gadobenate dimeglumine (MultiHance) in the absence and presence 4% HSA.<sup>30</sup> Note that for gadobutrol (Gadavist), as well as for all other nonprotein binding GBCAs, the presence of HSA has no effect on the relaxivity profiles. On the other hand, for gadobenate dimeglumine (MultiHance), the presence of HSA results in a notable spike in measured relaxivity precisely in the range (≈10-150 MHz) of magnetic

field strengths used in clinical practice (0.47T = 20 MHz; 3T = 127.5 MHz). It is this protein interaction, and resulting increased relaxivity, that likely explains results of intraindividual crossover studies demonstrating greater signal intensity and diagnostic performance for the high-relaxivity multipurpose GBCA gadobenate dimeglumine (MultiHance) vs other GBCAs in CNS,<sup>1-3</sup> breast,<sup>32</sup> and liver,<sup>33</sup> as well as for MRA of various vascular territories.<sup>34-38</sup>

### Clinical Considerations in GBCA Selection

Returning now to our 3 groups of agents, macrocyclic agents with standard relaxivity, linear agents with standard relaxivity, and linear agents with higher relaxivity, how does one select a GBCA for routine use applications?

**Table 5. Summary of recent prospective, intraindividual, neuroimaging crossover studies comparing 0.1 mmol/kg gadobenate dimeglumine (MultiHance) with an equal dose of comparator.<sup>1-3,47</sup>**

Study	Field Strength	Patients	Comparator	Results
Maravilla, 2006	1.5T	151 patients with brain or spine lesions	Gadopentetate dimeglumine (Magnevist)	Significantly (P≤0.001) higher overall reader preferences for gadobenate dimeglumine (MultiHance); significant (P≤0.0001) preference for gadobenate dimeglumine (MultiHance) demonstrated for diagnostic information endpoints, percentage of lesion enhancement, and CNR
Rowley, 2008	1.5T	126 patients with primary or secondary brain lesions	Gadodiamide (Omniscan)	Significantly (P≤0.0001) higher overall reader preferences for gadobenate dimeglumine (MultiHance); highly significant (P≤0.0001, all readers) preference for gadobenate dimeglumine (MultiHance) demonstrated for all qualitative endpoints and for CNR
Rumboldt, 2009	3T	41 patients with enhancing brain lesions	Gadopentetate dimeglumine (Magnevist)	Significantly (P≤0.0001) higher overall reader preferences for gadobenate dimeglumine (MultiHance); significant (P≤0.001) preference for lesion border delineation and enhancement with gadobenate dimeglumine (MultiHance)-enhanced images; significantly (P≤0.05) higher LBR, CNR, and percentage of lesion enhancement noted with gadobenate dimeglumine (MultiHance)
Seidl, 2012	1.5T	114 patients with known or suspected brain tumors	Gadobutrol (Gadavist)	Significantly (P≤0.0001) higher overall reader preferences for gadobenate dimeglumine (MultiHance); highly significant (P≤0.0001, all readers) preference for gadobenate dimeglumine (MultiHance) demonstrated for all qualitative endpoints and for CNR

**Table 6. Summary of recent prospective, intraindividual, crossover studies comparing GBCAs for MRA of various vascular territories.**<sup>38,47-53</sup>

Study	Field Strength	N	Territory	Comparator A	Comparator B	Results
Attenberger, 2008*	1.5T/3T	40	Renal vasculature	15 mL (0.2 mmol/kg) gadobutrol (Gadavist) at 1.5T	15 mL (0.1 mmol/kg) gadobenate dimeglumine (MultiHance) at 3T	Single dose gadobenate dimeglumine (MultiHance) at 3T yields comparable image quality to double dose gadobutrol (Gadavist) at 1.5T.
Buelmann, 2008	3T	12	Supra-aortic vessels	0.1 mmol/kg gadopentetate dimeglumine (Magnevist)	0.1 mmol/kg gadobenate dimeglumine (MultiHance)	Significantly better image quality and contrast enhancement achieved with gadobenate dimeglumine (MultiHance) at 3T.
Spampinato, 2010	1.5T	20	Spinal vessels	0.2 mmol/kg gadodiamide (Omniscan)	0.2 mmol/kg gadobenate dimeglumine (MultiHance)	Gadobenate dimeglumine (MultiHance) significantly superior ( $P<0.05$ ) to gadodiamide (Omniscan) in the representation of vascular continuity and contrast; 2 observers deemed overall quality of the gadobenate dimeglumine (MultiHance)-enhanced MRA superior in 15 and 16 cases, respectively.
Schneider, 2010	1.5T	39	Renal vasculature	0.3 mmol/kg gadofosveset trisodium (Ablavar)	0.1 mmol/kg gadobenate dimeglumine (MultiHance)	For first-pass images, significant superiority was noted with gadobenate dimeglumine (MultiHance) for specificity ( $P\leq 0.02$ ), accuracy ( $P\leq 0.005$ ), and PPV ( $P\leq 0.018$ ); steady-state images showed no benefit for gadofosveset trisodium (Ablavar).
Gerretsen, 2010	1.5T	92	Peripheral vasculature	0.1 mmol/kg gadopentetate dimeglumine (Magnevist)	0.1 mmol/kg gadobenate dimeglumine (MultiHance)	Gadobenate dimeglumine (MultiHance) provided higher-quality vessel visualization, greater contrast enhancement, fewer technical failures, and improved diagnostic performance.
Li, 2013	1.5T	46	Supra-aortic vessels	0.2 mmol/kg gadopentetate dimeglumine (Magnevist)	0.1 mmol/kg gadobenate dimeglumine (MultiHance)	No differences noted by any reader for any qualitative parameter; non-significant superiority for gadobenate dimeglumine (MultiHance) reported for sensitivity, specificity, accuracy, PPV, and NPV; no differences in quantitative enhancement noted.
Wang, 2013	1.5T	68	Peripheral vasculature	0.2 mmol/kg gadopentetate dimeglumine (Magnevist)	0.1 mmol/kg gadobenate dimeglumine (MultiHance)	No differences noted for any qualitative parameter at any station; nonsignificant superiority for gadobenate dimeglumine (MultiHance) reported for sensitivity, specificity, accuracy, PPV, and NPV; quantitative enhancement similar in pelvis but for 2 readers, significantly ( $P<0.05$ ) greater with gadobenate dimeglumine (MultiHance) in the thigh.

\*Attenberger et al, was an interindividual study; all others were intraindividual, crossover comparisons.

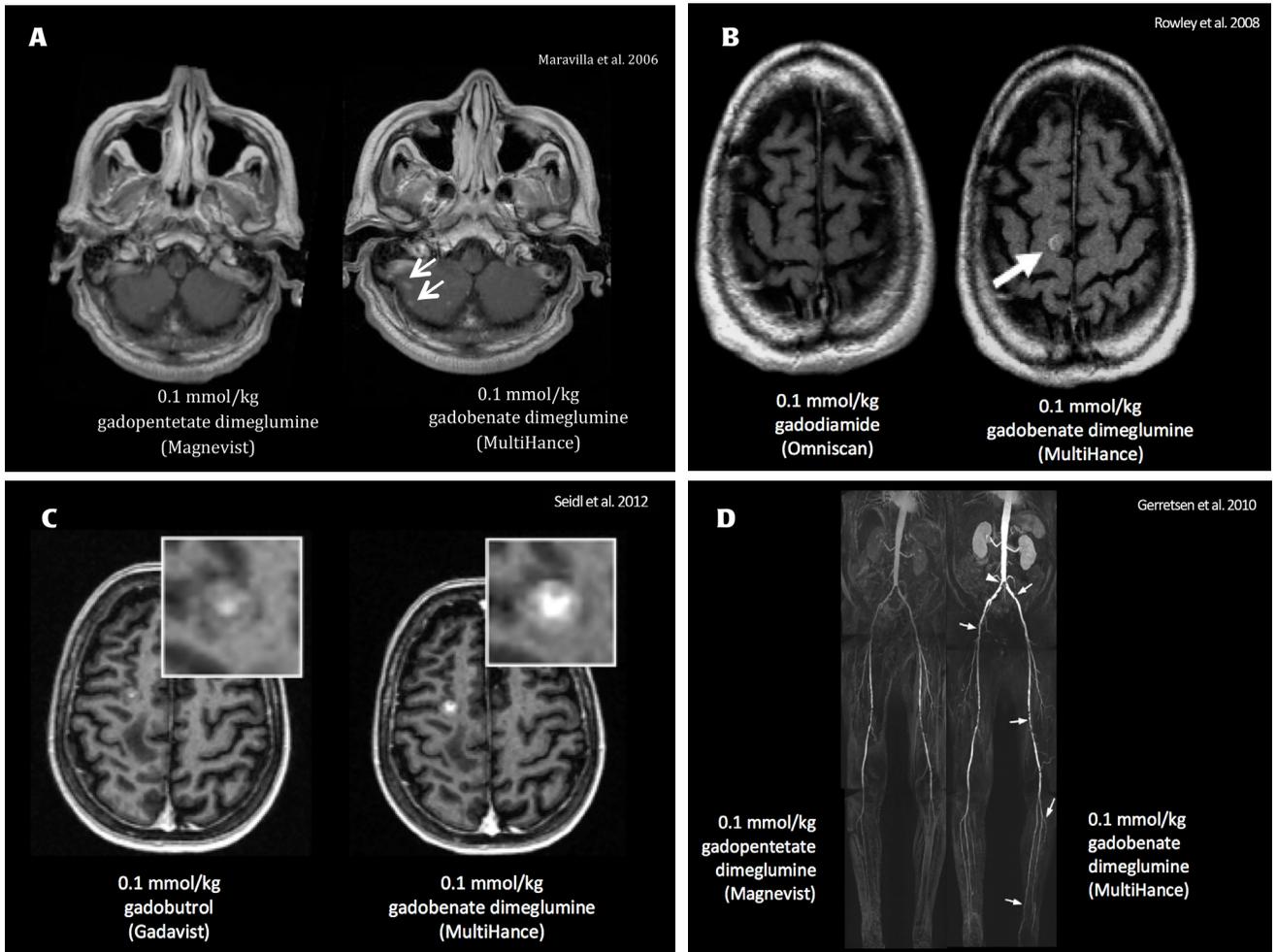


FIGURE 6. (A-D) Paired images from intraindividual crossover studies.<sup>1-3,38</sup>

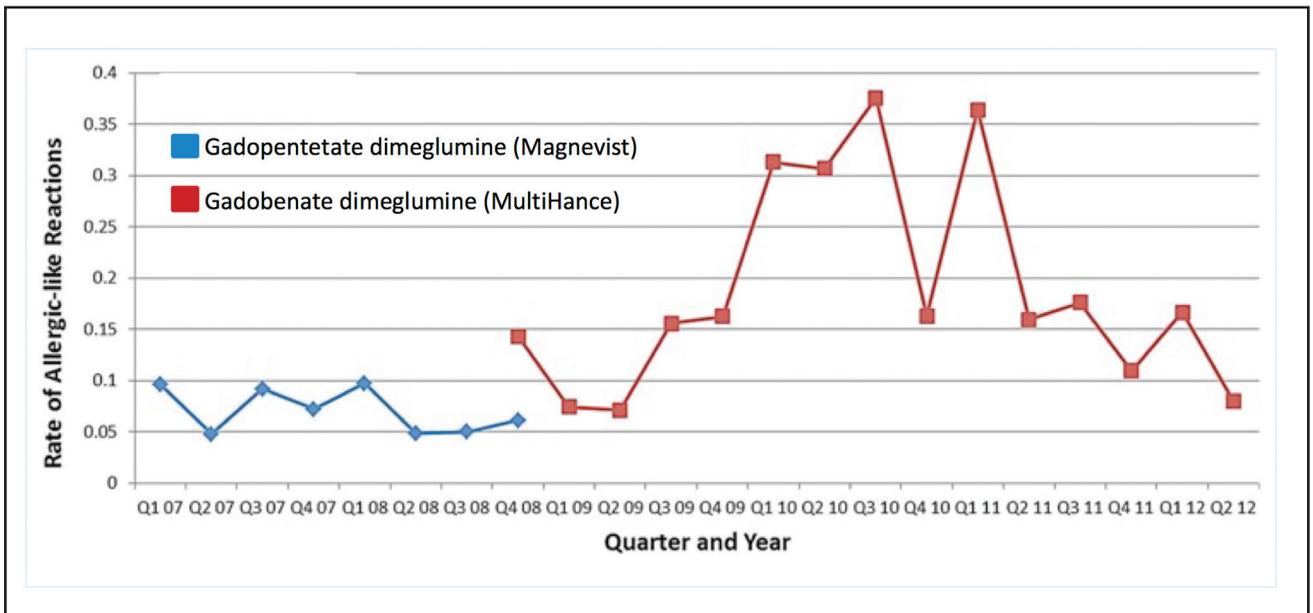
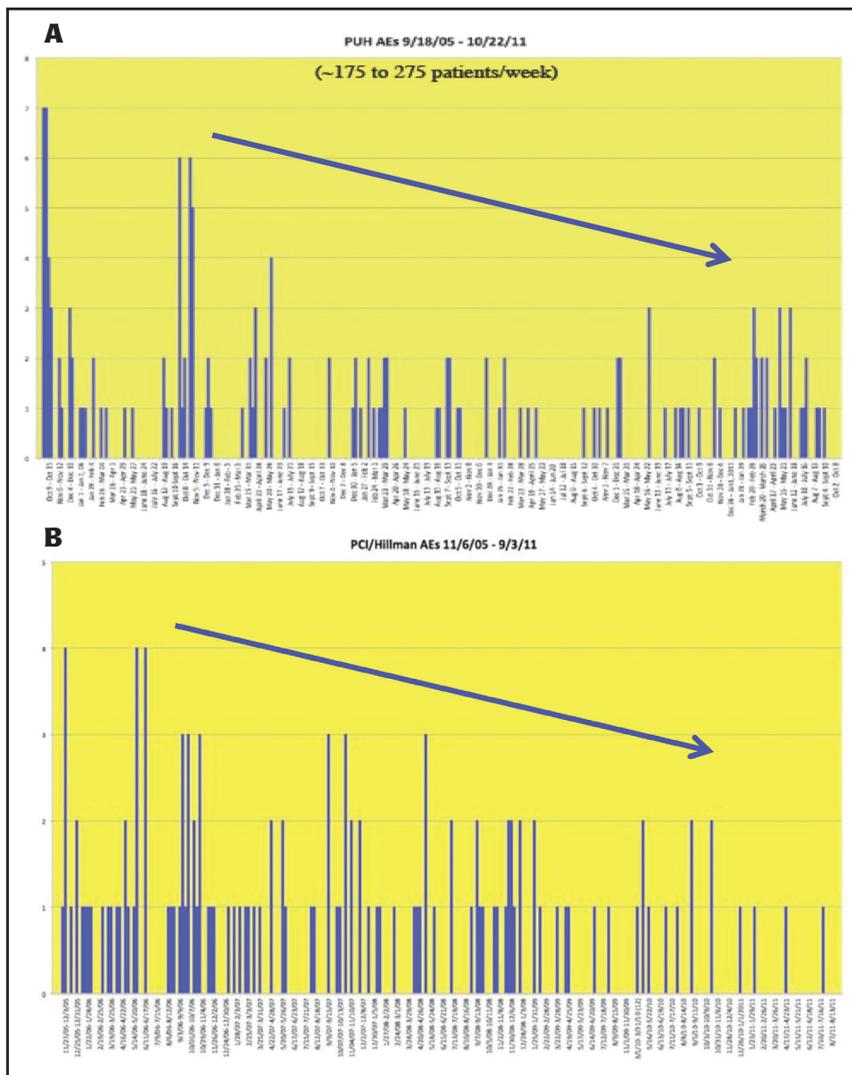


FIGURE 7. Quarterly rates of allergic-like reactions following administration of gadopentetate dimeglumine (Magnevist) and gadobenate dimeglumine (MultiHance).<sup>43</sup>

**Table 7. Adverse event rates with gadobenate dimeglumine (MultiHance) at UPMC sites.<sup>44,45</sup>**

UPMC site	# Patients	Patients receiving gadobenate dimeglumine (MultiHance) N (%)	Adverse reactions N (%)
PUH/MUH/CHP/Sports	33,559	13,552 (40)	63 (0.5)
SUH	8,821	3,624 (41)	44 (1.2)
Greenville	3,667	1,224 (33)	9 (0.7)
Shenango	2,738	772 (28)	6 (0.8)
Hillman/PCI	3,536	2,117 (60)	44 (2.1)
St. Margaret's	5,443	1,910 (35)	7 (0.4)
Southside	924	354 (38)	5 (1.4)
<b>TOTAL*</b>	<b>58,688</b>	<b>23,553 (40)</b>	<b>178 (0.8)</b>
<b>Updated Total** (PUH/MUH/SUH/PCI)</b>	<b>258,751</b>	<b>125,308 (48)</b>	<b>474 (&lt;0.4)</b>

\*Data from September, 2005 through November, 2006.  
\*\*Data from September, 2005 through October, 2011.



**FIGURE 8.** Adverse event rates reported each week at the (A) PUH site and the (B) PCI/Hillman site.<sup>45</sup>

**Efficacy**

It has been well established that greater relaxivity leads to higher signal intensity enhancement. Of the multipurpose linear agents, gadobenate dimeglumine (MultiHance) has the highest r1 relaxivity at 1.5T, and this high relaxivity persists at 3T.<sup>39</sup> Tables 5 and 6 summarize results from the most recent, robust intraindividual crossover studies comparing the efficacy of gadobenate dimeglumine (MultiHance) with standard relaxivity agents for MR imaging of the CNS (Table 5) and vasculature (Table 6). Examples of image pairs from published comparative studies are shown in Figure 6. From this body of evidence, one can conclude that at typical so-called T1-weighted imaging approaches, a single dose of gadobenate dimeglumine (MultiHance) is very roughly diagnostically equivalent to a double dose of a standard relaxivity agent, and that it provides better qualitative and quantitative diagnostic MR images when compared to an equivalent dose of a standard-relaxivity agent, for a variety of applications.

**Safety**

Regarding safety profiles, all of the GBCAs are considered to have low and comparable acute adverse event (AE) rates, regardless of whether the data are derived from product package inserts,<sup>12-20</sup> from clinical trial safety data,<sup>40</sup> or from professional society

**Group I: Agents associated with the greatest number of NSF cases:**

- Gadodiamide (Omniscan® – GE Healthcare)
- Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)
- Gadoversetamide (OptiMARK® – Covidien)

**Group II: Agents associated with few, if any, unconfounded cases of NSF:**

- Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
- Gadoteridol (ProHance® – Bracco Diagnostics)
- Gadoteric acid (Dotarem® – Guerbet)
- Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)

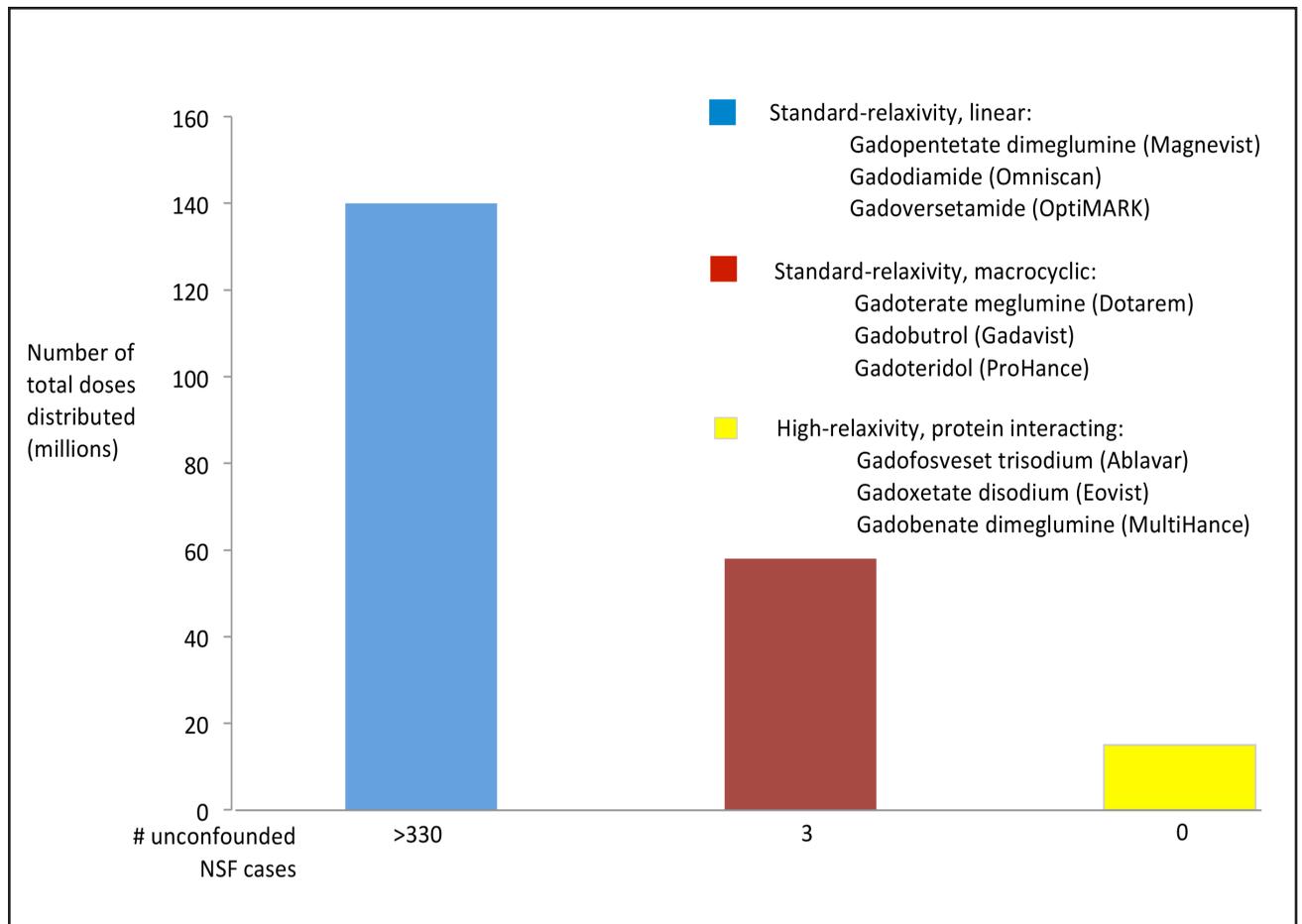
**Group III: Agents that have only recently appeared on the market:**

- Gadofosveset (Ablavar® – Lantheus Medical Imaging)
- Gadoxetic acid (Eovist® – Bayer HealthCare Pharmaceuticals)

guidelines.<sup>41</sup> The vast majority of AEs are mild, with the most common being transient injection site discomfort, nausea with or without vomiting, headache, paresthesia, dizziness, and itching.<sup>41</sup>

Upon adoption of a new drug, reported AE rates may go up initially but over time, tend to return to baseline. This was first observed by Weber in 1984 and has thus been termed the Weber effect.<sup>42</sup> Davenport and colleagues observed the Weber effect at their institution when switching from gadopentetate dimeglumine (Magnevist) to gadobenate dimeglumine (MultiHance).<sup>43</sup> Specifically, they noted that the reaction rates for gadobenate dimeglumine (MultiHance) peaked in the second year after it replaced gadopentetate dimeglumine (Magnevist), and then declined in the third year, ultimately returning to a baseline rate that did not differ significantly from the original baseline rate of gadopentetate

**FIGURE 9.** Classification of GBCAs according to NSF risk.<sup>41</sup>



**FIGURE 10.** Numbers of administered doses and unconfounded cases of NSF for each of the GBCA groups.

dimeglumine (Magnevist) (Figure 7). The reasons for the Weber effect are complex and not completely understood, but it is generally believed to be related to unfamiliarity with a new drug, or new contrast agent in this case, and/or concern from staff regarding the change.

Recently, the incidence of AEs was prospectively studied at 10 sites associated with the University of Pittsburgh Medical Center (UPMC).<sup>44</sup> A summary of the findings is shown in Table 7 and Figure 8. Most noteworthy is the gradual decline in AE rates over time, indicative of the Weber effect. Specifically, for data collected from 2005 through 2006, the overall AE rate was 178/23,553 (0.8%), but when the data collection was extended through 2011, the overall AE rate declined to 474/125,308 (< 0.4%).<sup>45</sup> The incidence of serious AEs from this prospective study with gadobenate dimeglumine (MultiHance) was much lower (8/23,553 [0.03%]) and similar to the incidence of serious AEs with gadopentetate dimeglumine (Magnevist; 1/4,892 [0.02%]), obtained retrospectively, consistent with a lack of Weber effect for serious AEs. In addition, during this same time period, the incidence of anaphylactoid events at UPMC was 0.004%, or approximately 4/100,000, a rate that is much lower than that observed with either high-osmolar iodinated contrast media ( $\approx$ 100/100,000) or low-osmolar iodinated contrast media ( $\approx$ 20/100,000).<sup>29</sup>

The most significant potential nonacute event associated with Gd exposure remains NSF. The factors most closely associated with the development of NSF include severe renal failure in the patient, exposure to multiple/high doses of a GBCA, and administration of a less stable GBCA.<sup>41,46</sup> However, the majority of patients with severe renal failure administered multiple and/or high doses of a relatively unstable GBCA do not develop NSF, so it is likely that there remain unidentified factors that contribute to the development of NSF.

Per the American College of Radiology, GBCAs can be grouped into

3 groups according to their NSF risk (Figure 9).<sup>41</sup> These groupings are based on the numbers of unconfounded, single-agent cases of NSF recorded for each agent. However, it is also interesting to examine the number of unconfounded NSF cases and the number of doses distributed, but to do so using the grouping system introduced in the introduction (Figure 10). When one does so, there are 2 apparent observations: first, and not surprisingly, the incidence of NSF with the macrocyclic agents is extremely low considering the number of administered doses and, second, that the number of NSF cases is surprisingly low in the group of intermediate-stability, protein-interacting GBCAs, including gadofosveset trisodium (Ablavar), gadoxetate meglumine (Eovist), and gadobenate dimeglumine (MultiHance), considering their number of administered doses, suggesting perhaps that there is something protective about protein binding that mitigates or prevents the development of NSF. Any evidence for such protection, or any possible mechanism, remains to be established.

## Conclusions

Chemical stability and in vivo relaxivity are the GBCA properties most relevant for selection of a contrast agent for MRI. Agents with a macrocyclic structure are the most highly stable and, as they do not bind to serum proteins, they all possess similar, relatively low relaxivity. Relatively lower stability linear agents may be of standard or high relaxivity. No cases of NSF have been reported after the prior unconfounded administration of any of the high-relaxivity protein interacting agents, the vascular imaging agent gadofosveset trisodium (Ablavar), the hepatic imaging agent gadoxetate meglumine (Eovist), or the CNS/multipurpose agent gadobenate dimeglumine (MultiHance). In terms of NSF, "low risk" does not appear to be equivalent to "no risk"; some level of caution is still warranted for all agents in the highest-risk patients.

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