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Gadolinium-based contrast agents: why nephrologists need to be concerned

Katarina Leyba[d] and **Brent Wagner**[a,b,c]

[a]Kidney Institute of New Mexico, Albuquerque, New Mexico, USA

[b]New Mexico Veterans Administration Health Care System, Albuquerque, New Mexico, USA

[c]Department of Medicine, University of New Mexico Health Care System, Albuquerque, New Mexico, USA

[d]University of New Mexico School of Medicine, Albuquerque, New Mexico, USA

Abstract

Purpose of review—The hegemony of gadolinium-based contrast agent-induced adverse events stretches beyond those who have renal impairment. 'Nephrogenic' systemic fibrosis is a misnomer: gadolinium-based contrast agents are *the* known trigger for the disease; kidney impairment is a risk factor. Impaired (*true*) glomerular filtration may be one catalyst for gadolinium-based contrast agent-induced adverse events, but it is increasingly evident that the same cluster of symptoms occurs in patients with normal renal function.

Recent findings—It has been known for nearly 30 years that gadolinium-based contrast agents distribute and are cleared according to a three compartment model. Single doses of gadolinium-based contrast agents can trigger 'nephrogenic' systemic fibrosis in nondialysis dependent patients. Manifestations have occurred years after exposure. Renal insufficiency alone is not an adequate explanation for nephrogenic systemic fibrosis, and the continuum of its symptoms with the adverse events reported by patients with normal renal function clearly indicate that the physiologic reactions are largely undefined.

Summary—Gadolinium-based contrast agents should be used with extreme caution.

Keywords

central nervous system; contrast media; fibrosis; gadolinium; patient safety (public health)

INTRODUCTION

There are 31.5 MRI machines per million people in the United States - five-fold that of England [1]. Millions of MRI studies are conducted annually; about half of these are

Correspondence to Brent Wagner, Director of the Kidney Institute of New Mexico, Renal Section Chief, New Mexico Veterans Administration Health Care System (501/111c), 1501 San Pedro Drive SE, Albuquerque, NM 87108, USA. Tel: +505 925 1065; BrWagner@salud.unm.edu.

Conflicts of interest

There are no conflicts of interest.

enhanced with gadolinium-based contrast agents [2]. The gadolinium ion, although a toxicant, is ideally suited for the clinical application of enhancing MRI because of its unique paramagnetic properties. Four-hundred and fifty million doses of gadolinium-based contrast agents have been administered since 1998 [3▪▪]. Sales of these agents are now at an all-time high. *Gadolinium-enhanced MRI is a staple of contemporary diagnostic medicine.*

Proprietary polyaminocarboxylate chelates have been formulated for pharmaceutical use to 'cage' the gadolinium (III) cation [4], thereby reducing the toxicity of the metal. There is a thermodynamic equilibrium of gadolinium with the ligand that forms the chelate:

$$\left[\mathrm{Gd}^{3+}\right] + [\mathrm{Ligand}] \rightleftharpoons \left[\mathrm{Gd}^{3+} \cdot \mathrm{Ligand}\right] \quad (1)$$

Each ligand has a different affinity for gadolinium, (the rate constants expressed as the logarithm of the thermodynamic stability, log (K_{therm}), measured *in vitro* and at nonphysiologic pH):

$$K_{\mathrm{therm}} = \frac{\left[\mathrm{Gd}^{3+} \cdot \mathrm{Ligand}\right]}{\left[\mathrm{Gd}^{3+}\right][\mathrm{Ligand}]} \quad (2)$$

The affinities for the ligands to form chelated complexes is very strong (albeit at nonphysiologic conditions), therefore these reactions proceed very strongly to the right of Eq. (1). The *conditional* thermodynamic stability, log (K_{cond}), predicts the equilibrium at a physiologic pH of 7.4 [5]:

$$K_{\mathrm{cond}} = \frac{\left[\mathrm{Gd}^{3+} \cdot \mathrm{Ligand}\right]}{\left[\mathrm{Gd}^{3+}\right][\mathrm{Ligand}]} \times \frac{[\mathrm{Ligand}]}{[\mathrm{protonated\ Ligand}]} \quad (3)$$

The agents are categorized by their general chemical structure (open-chain/linear or macrocyclic) and the overall charge, based on side chains (ionic or nonionic). Regardless of these characteristics, the log (K_{cond}) for these agents falls in the same range (Table 1).

In 2007, the market share for these agents was Magnevist (gadopentetate dimeglumine, Bayer, Leverkusen, Germany) >> Omniscan (96% gadodiamide/4% caldiamide, GE Healthcare, Princeton, NJ, United States) >> OptiMARK (92% gadoversetamide/8% calcium versetamide, Guerbet, Paris, France) > MultiHance (gadobenate dimeglumine, Bracco, Milan, Italy) > ProHance (gadoteridol, Bracco) (Fig. 1). The valence of the gadolinium (III) cation is either balanced by the number of carboxyl groups (i.e., nonionic: Gadovist, ProHance, OptiMARK, and Omniscan), or not (i.e., ionic: MultiHance, Dotarem, Eovist, Magnevist, and Ablavar).

WHO'S AFRAID OF 'NEPHROGENIC' SYSTEMIC FIBROSIS?

In 2000, Cowper *et al.* [6] reported a unique sclerotic skin condition in 15 patients with the common history of renal impairment (i.e., renal allograft recipients, maintenance hemodialysis, and one case of acute kidney injury). Skin was thickened and hardened extensively in regions atypical for systemic sclerosis. First characterized in patients with kidney disease, the disorder was initially christened 'nephrogenic fibrosing dermopathy' then 'nephrogenic systemic fibrosis' as evidence for multiorgan fibrosis accumulated [7–9]. In 2006, this incapacitating condition was correlated with gadolinium-based contrast agent exposure [10▪]. Therefore the adjective 'nephrogenic' is a misnomer [11]. Renal impairment is not the genesis of the disorder, but rather exposure to the gadolinium-based contrast agent. The compromised glomerular filtration rate may be either chronic (including end-stage renal disease) or acute. By March 2007, the United States Food and Drug Administration (FDA) issued a boxed warning cautioning that patients with impaired glomerular filtration rates (acute kidney injury or chronic kidney disease) exposed to gadolinium-based contrast agents were at risk for 'nephrogenic' systemic fibrosis [12].

The diagnostic criteria for 'nephrogenic' systemic fibrosis (Fig. 2) currently *do not include a history of gadolinium exposure* [13▪▪]. This was to improve the sensitivity of the diagnosis - the doses of gadolinium-based contrast agents, the types, or even whether they were administered have not always been well documented - and 'using the presence of documented prior gadolinium exposure as a positive predictor will create a self-fulfilling prophecy regarding the role of gadolinium' for causing 'nephrogenic' systemic fibrosis [13▪▪]. These criteria are nebulous with respect to renal impairment *and do not state a definitive threshold of kidney function required for the diagnosis*.[1] Several gadolinium-based contrast agents cause 'nephrogenic' systemic fibrosis. *The common variable,* though, *is gadolinium*.

The diagnostic criteria are heavily weighted on the unique histology of 'nephrogenic' systemic fibrosis: dermal hypercellularity and increased CD34 staining; CD34 is a marker of bone marrow-derived cells, some of which are thought to be 'fibrocytes' - circulating white blood cells that participate in wound healing by differentiating into myofibroblasts [14]. Patients with 'nephrogenic' systemic fibrosis demonstrate an increased number of spindle-shaped cells with markers of 'fibrocytes' - circulating, bone marrow-derived cells that can differentiate into α-smooth muscle actin-expressing myelofibroblasts that can deposit extracellular matrix [15]. Our team tested this experimentally with the first chimeric rodent model of 'nephrogenic' systemic fibrosis [16▪]. Recipients with 5/6 nephrectomy (to model chronic kidney disease) underwent lethal irradiation followed by bone marrow transplant from tagged donors. Omniscan treatment led to a great increase in myeloid cells in the skin concomitant with extracellular matrix deposition, α-smooth muscle actin expression, and fibrocyte cellular markers. The increase in dermal cellularity was identical to that seen in patients suffering from 'nephrogenic' systemic fibrosis [17]. Moreover, gadolinium-based

[1]The criteria state, 'Absence of documentable renal disease: in the unlikely event the final patient score falls into ["nephrogenic" systemic fibrosis box] yet current or prior renal cannot be established, the most certain [diagnosis] that should be rendered is "suggestive of" "nephrogenic" systemic fibrosis [13]. At the 2017 US FDA Medical Imaging Drugs Committee meeting *several* cases that scored within the "nephrogenic" systemic fibrosis criteria were among patients with normal renal function'.

contrast agent treatment increased the quantity of reactive oxygen species in the skin parallel with an increase of NAPDH oxidase type 4 (Nox4). When gadolinium-based contrast agent-treated animals concomitantly ingested a superoxide dismutase mimetic to quench the reactive oxygen species, there was a significant diminution of fibrosis. This was the first experimental proof that gadolinium-based contrast agents induce the migration of myeloid cells to areas of fibrosis and demonstrated that Nox4-derived reactive oxygen species may mediate the disease [4,16▪].

Bone marrow-derived fibrocytes invade the dermis either by activation of the bone marrow and attraction to affected regions or by the release of a chemoattractant - secondary to deposition of gadolinium-based contrast agent or the transchelated gadolinium - that recruits myeloid cells from the circulation. We tested this by ‘priming’ donor bone marrow with gadolinium-based contrast agent and then transplanting control or ‘primed’ marrow into lethally irradiated recipients (again with 5/6 nephrectomy). Although the ‘primed’ myeloid cells did not induce the disease *de novo*, recipients of this ‘primed’ marrow manifested more fibrosis when challenged with gadolinium-based contrast (compared with contrast-treated recipients of naive marrow). *Myeloid cells have a memory of prior gadolinium-based contrast agent exposure* [18▪]. This explains why the cumulative dose correlates with disease severity [19▪▪].

The American College of Radiology’s recommendations for the use of gadolinium-based contrast agents are organized according to chemical formulation and *presumed* patient risk [20]. Notably, however, *these guidelines are based largely on expert opinion and not on experimental evidence.* For instance, the assertion that ‘group II agents are strongly preferred in patients at risk for’ ‘nephrogenic’ systemic fibrosis is based on case series and case reports. *All of these studies are observational*, therefore hypothesis-generating at best [21,22].

It is important to note that there is a strong risk of representational bias within the current scientific literature on gadolinium-based contrast agents and ‘nephrogenic’ systemic fibrosis. In 2006, the market share of class II gadolinium-based contrast agents was only 7.6%, whereas the market share of class I agents (i.e., Omniscan and Magnevist) was more than 80% (Fig. 3). The FDA applied a boxed warning to all gadolinium-based contrast agents in 2007, protecting many (not all) high-risk patients from many gadolinium-based contrast agents [23].

All prescribing information materials for each of the gadolinium-based contrast agents warns of the risk for ‘nephrogenic’ systemic fibrosis.[2] The decline in cases of ‘nephrogenic’ systemic fibrosis after the FDA’’s 2007 boxed warnings against the use of gadolinium-based

[2]The prescribing information for Dotarem states, ‘Gadolinium-based contrast agents… increase the risk for [“nephrogenic” systemic fibrosis] among patients with impaired elimination of the drugs. Avoid use of [gadolinium-based contrast agents] in these patients unless the diagnostic information is essential and not available with non-contrasted [magnetic resonance imaging] or other modalities. [“Nephrogenic” systemic fibrosis] may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.’ This same statement is in the prescribing information for ProHance [log (K_{therm}) 23.8], Eovist [log (K_{therm}) 23.5], Magnevist [log (K_{therm}) 22.5], MultiHance [log (K_{therm}) 22.2], Ablavar [log (K_{therm}) 22.1], Gadovist [log (K_{therm}) 21.8], Omniscan [log (K_{therm}) 16.9], and OptiMARK [log (K_{therm}) 16.8]. The US FDA has yet to endorse any one brand of gadolinium-based contrast agent over another with this specific warning.

contrast agents in the setting of renal insufficiency demonstrates the impact on clinical practice. It would be sophistic to conclude that the newer gadolinium-based contrast agents approved for clinical use after 2007 are 'nephrogenic' systemic fibrosis inert because risk-averse diagnosticians have been reluctant to administer these to high-risk patients (despite recommendations to the contrary).

Prescribing information warnings that caution against the use of gadolinium-based contrast agents in high-risk patients are no guarantee that such a population is safe. For instance, a 2018 publication from the Department of Medical Imaging at the University of Arizona College of Medicine, Banner University Medical Center in Tucson, defiantly titled, 'No incidence of nephrogenic systemic fibrosis after gadobenate dimeglumine [MultiHance] administration in patients undergoing dialysis or those with severe chronic kidney disease' [24], was rapidly withdrawn 'because the study was not conducted in full accordance with the relevant institutional IRB protocol'. This was a retrospective analysis of nearly 4000 high-risk patients (i.e., severe chronic kidney disease or end-stage renal disease) exposed to MultiHance (an open-chain, high log K_{therm} agent). The cohort included 2000 individual hemodialysis patients, four-hundred and five peritoneal dialysis patients, and over 1000 severe chronic kidney disease patients. Again, this was a retrospective analysis, because to have exposed so many high-risk patients to gadolinium-based contrast agent in defiance of the FDA boxed warning[3] would have been perverse. These were not nonconsenting test participants, but patients who were exposed to gadolinium-based contrast agents during routine medical care. Given that manifestations of 'nephrogenic' systemic fibrosis can occur 8 years after exposure, not many investigators would have chanced deliberate exposure of so many high-risk patients to any gadolinium-based contrast agent. Although none of the authors had any conflicts of interest to disclose, it was noted that the institution 'received an unrestricted training fund grant from Bracco Diagnostics', the company that markets MultiHance. This highlights the degree to which patients with renal impairment are exposed to gadolinium-based contrast agents, even in academic centers.

WHO'S AFRAID OF NEPHROTOXICITY?

Despite evidence to the contrary, gadolinium-based contrast agents, when used at the label doses for MRI, are incorrectly assumed to be nonnephrotoxic. Therefore, up until 2006, it was common to use contrast-enhanced MRI instead of iodinated contrast-enhanced imaging in patients deemed to be at high risk for contrast-induced nephropathy [25]. In fact, gadolinium-based contrast agents are not less nephrotoxic than iodinated contrast [25]. Acute renal failure is an adverse reaction that is listed in the prescribing information for MultiHance, Dotarem, Magnevist, ProHance, Omniscan, OptiMARK, and Eovist. Angiographic MRI with gadolinium-based contrast agent enhancement (0.2 ml/kg) has been associated with acute renal failure (defined as a creatinine increase of 0.5 mg/dl in a retrospective analysis) in 12% of patients with chronic kidney disease stages 3–4 [26]. Another retrospective analysis [27] - using a very strict definition of acute renal failure (an increase in serum creatinine of more than 1.0 mg/dl within 48 h of exposure *and*

[3]'Labeling for *all* approved [gadolinium-based contrast agents] contains a boxed warning about "nephrogenic" systemic fibrosis in patients with impaired renal function who receive' gadolinium-based contrast agents [3].

concomitant oligoanuria) - found a correlation between gadolinium-based contrast agent-induced renal insufficiency when baseline creatinine clearances were less than 80 ml/min/1.73 m^2 (i.e., *mild* renal impairment).

WHO'S AFRAID OF GADOLINIUM RETENTION?

During the 8 September 2017 meeting of the FDA Medical Imaging Drugs Advisory Committee, it was commented that r*enal insufficiency seemed to be a catalyst for adverse reactions to gadolinium-based contrast agents*, but there are a number of people with normal kidney function who have met the diagnostic criteria for 'nephrogenic' systemic fibrosis. In rodent studies, renal impairment is not requisite to model the disease. Gadolinium-based contrast agents, most of which are cleared by the kidneys, have a volume of distribution similar to that of iodinated contrast: that is, largely the plasma space. However, gadolinium-based contrast agents *are not completely eliminated even in the setting of normal renal function*.

Autopsy studies demonstrate that gadolinium is retained in numerous organs [28] including the nuclei of neuronal cells of the central nervous system [29▪]. Gadolinium retention in specific brain areas seems to correlate with an increased (T1 weighted) signal on *unenhanced* brain MRI (particularly in the dentate nucleus and globus pallidus [30]). Gadolinium has been detected in the cerebellum, dentate nucleus, basal ganglia, frontal lobe of the cerebrum, and pons 764 days after exposure to a label dose of a gadolinium-based contrast agent [31]. (At present, the clinical consequences of gadolinium-based contrast agent retention in the brain have not been well defined.) Gadolinium concentrations are even higher in the bone, skin, liver, and kidney after exposure to these contrast agents. *There is ample evidence that the pharmacokinetic elimination of gadolinium-based contrast agents follows a multi-compartmental model* [32]. After an administration of gadolinium-based contrast agent, not all of it will be fully excreted.

Does hemodialysis eliminate all of the gadolinium-based contrast agent after exposure? Can hemodialysis be used as prophylaxis? Should gadolinium administration be timed with the hemodialysis schedule? [33].

There is *no evidence* that hemodialysis after exposure to gadolinium-based contrast agents (whether in chronic kidney disease stage 4 or 5 or in a patient on maintenance dialysis for end-stage renal disease) *has any impact on reducing the risk for complications*. Adverse reactions - including'nephrogenic' systemic fibrosis - are too rare to study the impact of prophylactic hemodialysis in a clinical setting. Delayed manifestations of 'nephrogenic' systemic fibrosis have occurred weeks after initiation of hemodialysis [34]. The threshold of exposure needed to trigger disease is completely undefined. Because some patients have had multiple exposures to gadolinium-based contrast agents and have not manifested symptoms, yet others acquire the full-blown systemic condition after just one dose indicates that there are lurking risk factors for 'nephrogenic' systemic fibrosis regardless of the cumulative dose. The evidence that gadolinium-based contrast agents seep into multiple slow-release compartments - including within the nuclei of neuronal cells - is colossal. These are protected compartments in which gadolinium-based contrast agents are not amenable to

elimination by hemodialysis (or chelation, in the case of normal renal function). *This is why it is requisite to discover the mechanisms of gadolinium-based contrast agent-induced disease.*

CONCLUSION

Gadolinium-based contrast agents are no less nephrotoxic than iodinated contrast [25], therefore it cannot be argued that the former should be preferable than the latter when contrast-induced nephropathy is a concern. Much of what has been published regarding the adverse effects of gadolinium-based contrast agents - either in narrative reviews or scientific work - has been by counterparts of the pharmaceutical industry or those who have profited from its vendors. Until the pathophysiology of gadolinium-based contrast agent-induced diseases is better defined, alternative imaging modalities without gadolinium should be considered when possible. Since the FDA boxed warning - because the label applied to *all gadolinium-based contrast agents, even the new ones* - subjecting a patient with renal impairment to gadolinium is essentially malpractice, therefore fewer at-risk patients have been exposed to the newer agents.

The issue of adverse events from gadolinium-based contrast agents has been obfuscated by the endeavors of pharmaceutical companies and their counterparts to disparage patients and to defang scientists. They must reluctantly admit that the biologic activity of these agents and the resultant adverse reactions abide by the laws of nature. Our attention should concern the *unknown* unknowns. Gadolinium-based contrast agents, for a fact, cause ‘nephrogenic’ systemic fibrosis. Renal impairment is a catalyst. The experimental evidence demonstrates that gadolinium-based contrast agents are biologically active - that is, *not inert*. Because single doses can trigger the disease, because patients with chronic kidney disease (i.e., not on dialysis) can contract ‘nephrogenic’ systemic fibrosis, and because this disease can begin to manifest *years* after exposure, all of us need to be gravely concerned about what threshold of gadolinium-based contrast agent can trigger the disease. If gadolinium is being liberated from the ligand, and if this is a necessary step for the disease, then how many atoms of gadolinium does it take? Parsing the question in this way should raise concerns about *all* gadolinium-based contrast agents because the thermodynamic stability constants are a probabilistic measurement.

Next, because some dialysis patients do not succumb to the disease even after multiple exposures, there are certainly other lurking risk factors ripe for discovery. Prospective clinical studies to determine the glomerular filtration rate (GFR) at which ‘nephrogenic’ systemic fibrosis is more likely to occur would be unnecessarily dangerous, therefore to formulate opinions about the degree of renal impairment in which exposure is safe is absolutely groundless. Because these compounds are biologically active *in vitro* and *in vivo*, and in the face of patients with normal renal function who report adverse events that overlap those of ‘nephrogenic’ systemic fibrosis (i.e., rash, muscle/tendon ‘tightness’, pain…), and because the other risk factors are undetermined, we need to be open to the possibility that ‘nephrogenic’ systemic fibrosis and these gadolinium-based contrast agent-induced symptoms are part of a continuum.

Radiologists are approaching the use of gadolinium-based contrast agents in a manner similar to how the tobacco industry treated their products. Instead, it should be acknowledged that none of the classes of gadolinium-based contrast agent strictly obeys two-compartment pharmacokinetic elimination; exposure equates to gadolinium-containing chemicals diffusing into compartments, including the brain and intracellular accumulation. Every administration of gadolinium-based contrast agent has the potential of inducing chronic adverse effects, including 'nephrogenic' systemic fibrosis. The view that the threshold of 'nephrogenic' systemic fibrosis directly correlates with renal impairment is sophistic. The converse should be held: for an undetermined reason, patients with normal renal function seem to have some protection against 'nephrogenic' systemic fibrosis, but it should not be assumed that this subset is entirely safe.

The recent American College of Radiology Manual on Contrast Media Version 10.3 warns that '[e]ach time a gadolinium-enhanced MRI study is considered, it would be prudent to consider the clinical benefit of the diagnostic information or treatment result that MRI or MRA may provide against the unknown potential risk of gadolinium deposition in the brain for each individual patient' [35].

The recommendations that are currently attempting to influence clinical decision-making are founded in opinion, not fact. There are broader risks than just 'nephrogenic' systemic fibrosis in kidney disease patients (regardless of acuity or stage). There is no prospective, randomized, and controlled trial evidence that some gadolinium-based agents are safer than others, particularly during an era when it is malpractice to use these in the setting of renal impairment. Patient care decisions should not be based on opinion grounded in fragmented evidence, especially when the potential risks are so incapacitating whether concerned about 'nephrogenic' systemic fibrosis or the untoward effects of long-term deposition of a toxic rare earth metal in nonvestigial organs (e.g., the skin, the bone, the brain). Given the ubiquity of gadolinium-based contrast agent usage, there is a pressing need for empirical, experimental data to inform clinical guidelines. *Until such research is conducted, we must be cautious about the use* gadolinium-based contrast agents *in patients at any level of renal function.*

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KEY POINTS

- All recommendations concerning the safety of gadolinium-based contrast agents, particularly in patients with acute or chronic renal insufficiency, are based in opinion; not prospective, experimental evidence.
- Gadolinium-based contrast agents, regardless of their chemical composition, are not eliminated according to a pure two compartment model; every brand seeps into slow-release compartments such as the blood brain barrier (and gadolinium has been found within the *nuclei* of central nervous system neurons).
- Because of delayed elimination, label dose administration of gadolinium-based contrast agents equate to multiple administrations in patients with renal insufficiency whether acute or chronic.
- Physiologically, there is no definite boundary between an *estimated* glomerular filtration of 46 ml/min/1.73 m^2 and 44 ml/min/1.73 m^2 that provides a mechanistic explanation for why ‘nephrogenic’ systemic fibrosis does or does not occur; nephrologists, then, are obliged to advocate for their patients against liberal application of gadolinium-based contrast agents regardless of the brand.
- Gadolinium is not a physiologic metal - none of the rare earth elements are; the consequences of long-term retention in any tissue are ill-defined therefore prudence dictates that use of gadolinium-based contrast agents be reduced to a minimum.

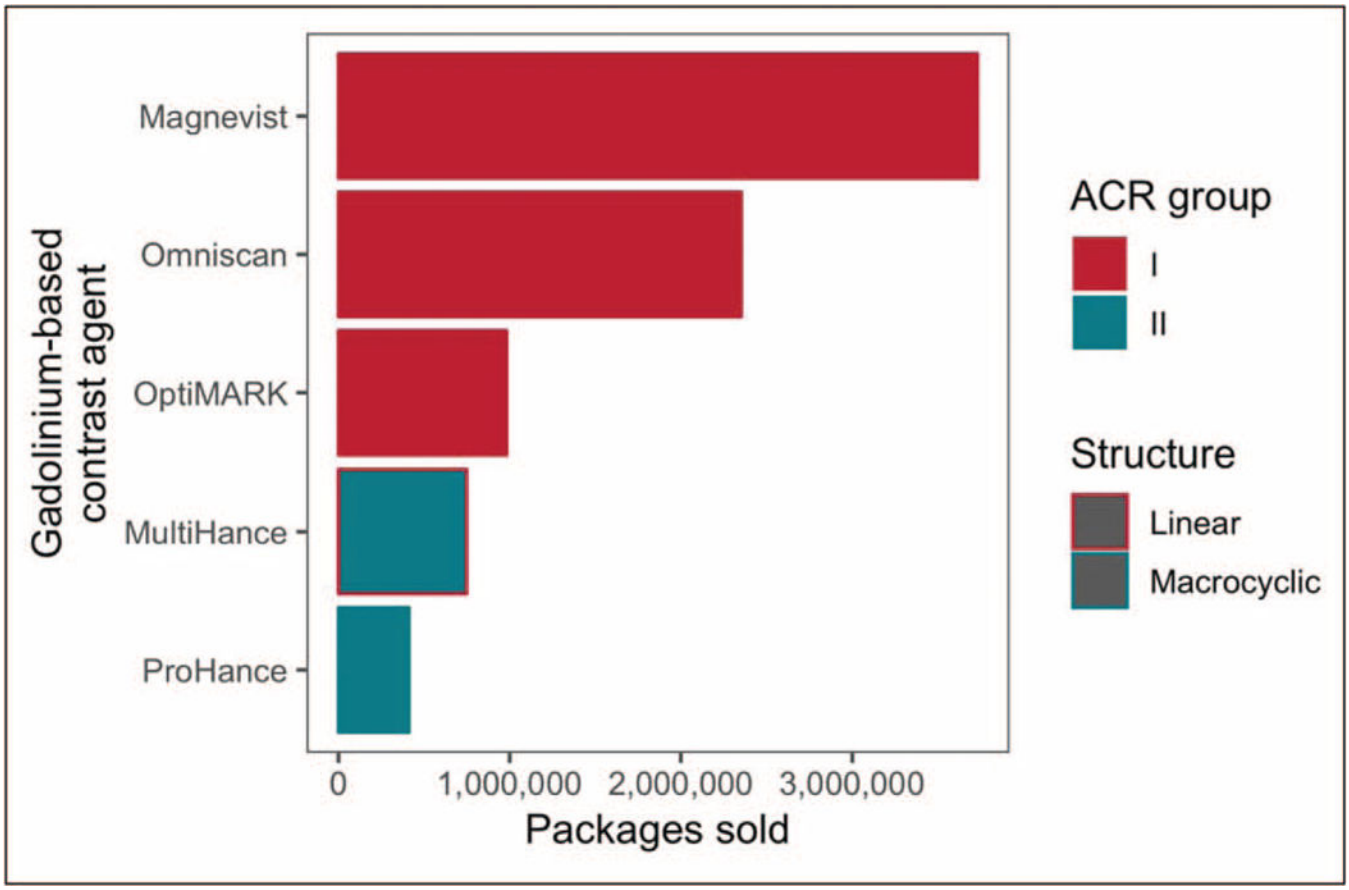

FIGURE 1.

National estimates for sales of gadolinium-based contrast agents in 2007. The Food and Drug Administration boxed warning cautioning against the use of gadolinium-based contrast agents was on 23 May 2007. Note that this boxed warning remains in the prescribing information *for all gadolinium-based contrast agents regardless of chemical structure or valence.* The American College of Radiology - based only on retrospective case reports and case series - categorized gadolinium-based contrast agents into three groups: group I, agents with the greatest number of 'nephrogenic' systemic fibrosis cases; group II, agents associated with 'few, if any unconfounded cases' of 'nephrogenic' systemic fibrosis; and group III, 'agents for which data remains limited regarding ('nephrogenic' systemic fibrosis) risk, but for which few, if any unconfounded cases of ('nephrogenic' systemic fibrosis) have been reported'. Note that group II agents (MultiHance and ProHance) represented a small market share (9 and 5%, respectively) when 'nephrogenic' systemic fibrosis was linked to gadolinium-based contrast agents and none of the group III agents were being used to any significant degree.

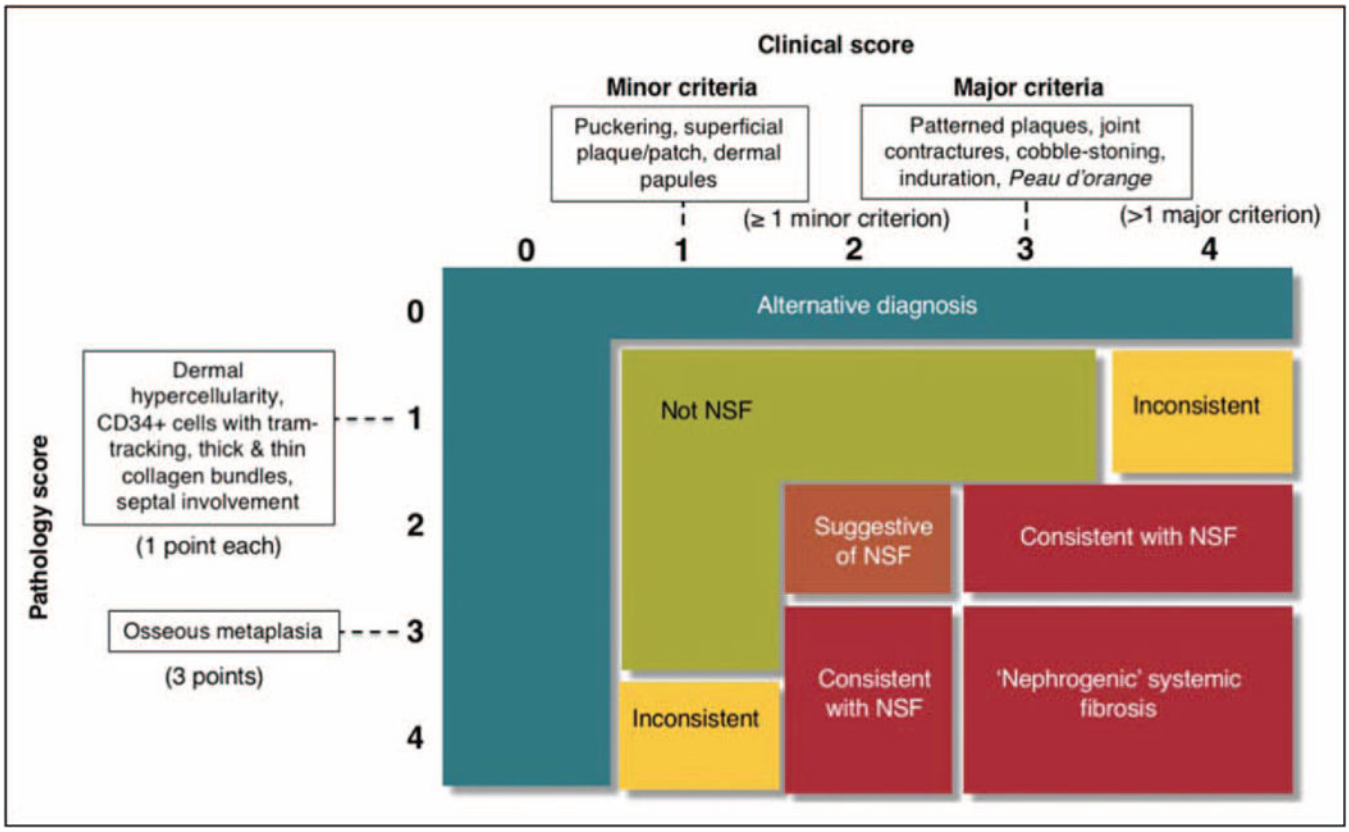

FIGURE 2.

The Girardi *et al.* criteria for the diagnosis of 'nephrogenic' systemic fibrosis. 'Nephrogenic' is a misnomer because renal insufficiency seems to be a *catalyst* for the disease, whereas the genesis is certainly gadolinium-based contrast agent exposure [11]. The diagnostic criteria are based on clinical and histopathologic scores [13▪▪]. The degree of renal impairment is not part of the diagnostic criteria. A history of exposure to gadolinium-based contrast agents is not part of the diagnostic criteria. NSF, 'nephrogenic' systemic fibrosis.

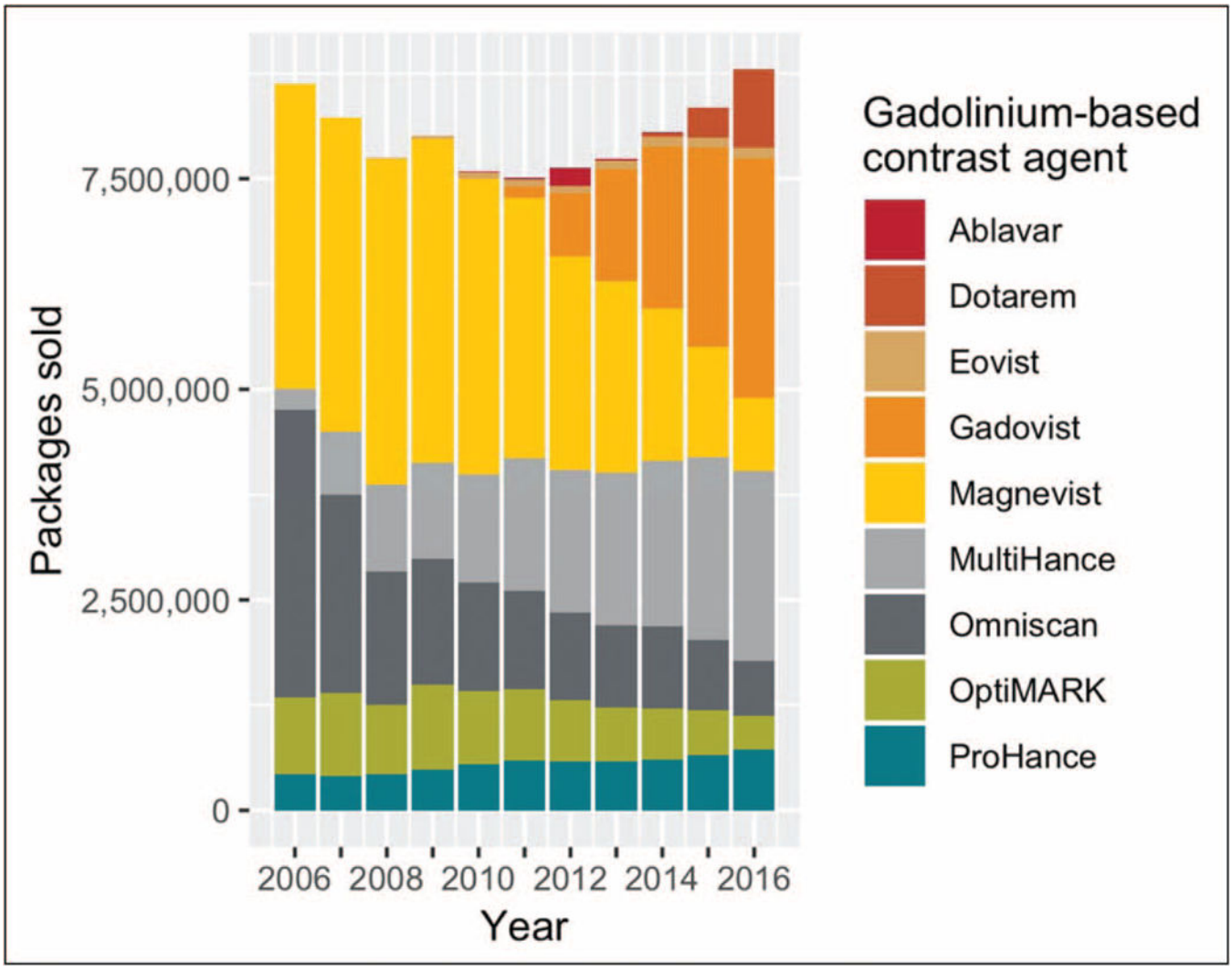

FIGURE 3.

Market share of gadolinium-based contrast agents (in packages sold) from US manufacturers to nonretail channels of distribution. Adapted from [3▪▪].

Table 1.

Types of gadolinium-based contrast agents approved for use in the United States

Generic name	Brand name	log (K_{cond})	United States approval year
Gadopentetate dimeglumine	Magnevist	17.7	1988
Gadodiamide	Omniscan	16.9	1993
Gadoversetamide	OptiMARK	15	1999
Gadoteridol	ProHance	17.1	2003
Gadobenate dimeglumine	MultiHance	18.4	2004
Gadoexetic acid	Eovist	18.7	2008
Gadofosveset trisodium	Ablavar		2008
Gadobutrol	Gadovist	17.1	2011
Gadoterate meglumine	Dotarem	19.3	2013