# Nephrogenic Systemic Fibrosis

Jeffrey C. Weinreb, MD[a,b,*], Phillip H. Kuo, MD, PhD[c,d]

**KEYWORDS**

• Gadolinium • Nephrogenic systemic fibrosis
• Gadolinium-based contrast agent • MR imaging
• MR contrast agents • Gadolinium chelates

Intravenous gadolinium-based contrast agents (GBCAs) are used commonly for MRI to aid in the detection, characterization, and staging of disease. For magnetic resonance angiography (MRA), many radiologists have become reliant on these agents because their use facilitates production of reliable, high-quality, higher spatial resolution, and time-efficient examinations. Furthermore, because their use previously was considered almost risk-free, GBCA-enhanced MRA often was preferred to contrast-enhanced digital subtraction angiography or CT angiography, which use intravenous iodinated contrast agents.

Until recently, there was general agreement that GBCAs were especially valuable for imaging vascular structures in patients who have compromised renal function, because they are less likely than iodinated agents to cause contrast-induced nephropathy. They commonly were administered generously, and sometimes indiscriminately, with very little concern about adverse events or renal function status, despite cautions from the manufacturers. Screening patients for chronic kidney disease (CKD) was thought to be unnecessary and was not considered the standard of care. In 2006, however, there were reports of an association between GBCAs and a rare, debilitating, and sometimes fatal disease called "nephrogenic systemic fibrosis" (NSF), and it was suggested that intravenous GBCAs might serve as a trigger for NSF.[1–3]

Subsequent publications and self-reported data received by the US Food and Drug Administration (FDA) Medwatch program seemed to validate the epidemiologic association of NSF with the administration of GBCAs in patients who had renal disease, and the FDA issued a Public Health Advisory on June 9, 2006.[4] Since then, the evidence for an association between GBCAs and NSF has continued to build and has had a considerable impact on the use of contrast-enhanced MRA, especially in patients who have kidney disease. Virtually unknown to the radiology community before 2006, NSF has generated concern and confusion among radiologists, clinicians, and their patients. In the relatively brief time since the emergence and recognition of NSF, policies have been developed, modified, and re-modified as the medical and legal communities seek to gain a better understanding of the disease and its apparent association with GBCA administration.

This article addresses the relationship between GBCAs and NSF and answers some common

J.C.W. has received research support and has served as a consultant and speaker for GE Healthcare and Bayer Healthcare Pharmaceuticals.

[a] Department of Diagnostic Radiology, Yale University School of Medicine, 333 Cedar Street, P.O. Box 208042, New Haven, CT 06520-5913, USA
[b] Body Imaging and MRI, Yale-New Haven Hospital, 333 Cedar Street, P.O. Box 208042, New Haven, CT 06520-5913, USA
[c] Department of Medicine, Section of Hematology/Oncology, University of Arizona, 1515 N. Campbell Avenue, P.O. Box 245024,Tucson, AZ 85724-5024, USA
[d] Department of Radiology, Southern Arizona Veterans Administration Hospital, 1515 N. Campbell Avenue, P.O. Box 245024, Tucson, AZ 85724-5024, USA
* Corresponding author. Department of Diagnostic Radiology, Yale University School of Medicine, 333 Cedar Street, P.O. Box 208042, New Haven, CT 06520-5913.
*E-mail address:* jeffrey.weinreb@yale.edu (J.C. Weinreb).

Magn Reson Imaging Clin N Am 17 (2009) 159–167
doi:10.1016/j.mric.2009.01.003
1064-9689/09/$ – see front matter 

questions. A more detailed discussion of clinical manifestations, epidemiology, pathogenesis, pathology, and treatment of NSF is beyond the scope of this article.

## WHAT IS NEPHROGENIC SYSTEMIC FIBROSIS?

NSF, initially called "nephrogenic fibrosing dermopathy" (NFD), was observed first in 1997, when patients in a hemodialysis center were noted to suffer progressive dermal hardening and thickening and erythema of the limbs, often accompanied by pruritus and sometimes pain. The lower extremities were affected more severely than the upper extremities. On histologic examination, the affected skin was characterized by profound fibrosis, sometimes with mucin deposition but no inflammatory infiltrates or paraprotein, one of the main features that distinguished NFD from scleromyxedema. The first cases were reported in 2000.[5,6]

Over time, as it became apparent that NFD was not merely a cutaneous process but a systemic one involving noncontiguous tissues and organs such as the heart, pericardium, diaphragm, pleura, kidneys, and testes, the disease was renamed "nephrogenic systemic fibrosis." The precise pathophysiology of NSF remains an active area for research and speculation, but it seems to be related to the administration of GBCAs to patients who have renal compromise.

## WHAT ARE GADOLINIUM-BASED CONTRAST AGENTS?

Gadolinium is a rare earth metal in the lanthanide series. In the 3+ oxidation state gadolinium has seven unpaired electrons that can interact with nuclear spins and cause a decrease in relaxation times of fluids and tissues. This ability to shorten the T1-relaxation time, or paramagnetism, makes gadolinium attractive for use in MR contrast agents, because its presence increases signal intensity on T1-weighted images. Free gadolinium itself, however, is highly toxic, in part because it is approximately the same size as a calcium ion and can block calcium channels and inhibit calcium-dependent enzymes. Thus, when gadolinium is used in intravenous MR contrast agents, the gadolinium ion is bound to an organic moiety (ligand) to form a metal-chelate complex. This binding results in an adequate safety profile while maintaining the favorable paramagnetic qualities. The gadolinium-chelate complex and varying amounts of chelating agent (depending upon the particular brand) then are dissolved in water to produce the GBCA formulation used in contrast-enhanced MRI/MRA.

In 2008, there were six FDA-approved GBCAs are commercially available in the United States, and several other GBCAs are in use in other parts of the world (**Table 1**). All these agents contain a gadolinium-chelate, but the ligand is different in each. Some have a linear structure, others are macrocyclic, and each has a unique constellation of stability constants and kinetics.

Gadobenate dimeglumine has a higher relaxivity than the extracellular agents that have been in use for MRI/MRA in the United States and may be used in smaller doses for certain applications, especially at a magnetic field strength of 3 T.[7–9] Gadobenate dimeglumine and gadoxetate disodium have some specific hepatobiliary uses. Nevertheless, the general attributes of the various GBCAs for MRA are comparable (even if they are not approved by the US FDA for this application). There are, however, two properties that have drawn considerable attention because they seem to be related— stability and safety.

Stability refers to how tightly the gadolinium ion is bound to the chelating molecule and the likelihood that it will dissociate. When dissociation occurs, the released gadolinium ion is picked up by a variety of competing anions and cation-binding proteins in the circulating blood. Overall, other factors being equal, the rates of dissociation of gadolinium are orders of magnitude slower from macrocyclic ligands than from linear ones, and macrocyclic ligands therefore are the most "stable."[10] There is evidence suggesting that the propensity to dissociate is related in some way to the induction of fibrosis in NSF. The exact mechanism has not been elucidated or firmly established, but circulating fibrocytes[11] and "free gadolinium" have been implicated.[3,12]

## WHAT IS THE RELATIONSHIP BETWEEN GADOLINIUM-BASED CONTRAST AGENTS AND NEPHROGENIC SYSTEMIC FIBROSIS?

In 2006, Grobner[2] published the first report of cases of NSF associated with GBCA exposure, and subsequent studies seemed to confirm the association, indicating that the risk of a patient who has renal disease contracting NSF following an exposure to GBCA varies widely, depending on the particular agent used, the dose, patient population, and the methodology of the study. For example, one retrospective study found no cases of NSF in 74,124 patients who were not screened for renal disease and who received a standard (single) dose of GBCA, mostly gadodiamide and gadopentetate dimeglumin.[13] Another study showed that 0.77% of dialysis patients who underwent GBCA-enhanced MRI developed