Nephrogenic Systemic Fibrosis

Jeffrey G. Penfield, M.D.
Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center

July 20, 2007

This is to acknowledge that Dr. Penfield has disclosed no financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Penfield will be discussing off label uses in his presentation.

Jeffrey G. Penfield, M.D.
Assistant Professor of Internal Medicine
Department of Medicine
Division of Nephrology
University of Texas Southwestern Medical Center
Veterans Affairs North Texas Healthcare System

Dr. Penfield is responsible for managing the Dallas VA renal clinic. His academic and clinical interests include post transplant hypophosphatemia, hypertension, anemia of renal disease, renal histopathology and nephrogenic systemic fibrosis.

Introduction:

Nephrogenic systemic fibrosis is a new disease. The first case was seen in 1997 and the first published description by Cowper did not appear until 2000.[1] The original name for this disorder was nephrogenic fibrosing dermopathy based on the predominant skin findings. As more severe cases emerged and autopsy cases were reviewed it became evident that this is a systemic disease and the name changed to nephrogenic systemic fibrosis (NSF) in 2005.[2] NSF is a rare disease with only 215 cases reported in a worldwide registry at Yale University.[3] It is seen exclusively in patients with decreased renal function (acute or chronic) and the majority of these patients were on dialysis when they developed the disease.

This rare disease limited to patients with renal disease became relevant to non-nephrologists when the link to gadolinium was established in January of 2000. No etiology had been established prior to this publication. Grobner *et al.* in Austria reported 5 patients out 9 who received a gadolinium containing contrast agent developed NSF.[4] This initial report was followed up by a report from the Danish Medicines Agency in May of 2006 that included the initial 5 Austrian cases and 20 more Danish cases linking the use of gadolinium to NSF.[5] The report stated that gadodiamide (the agent used in all 25 cases) was contraindicated in patients with a glomerular filtration rate (GFR) of less than 30 ml/min/1.73m^2 and the other gadolinium containing agents should be used with caution in patients with kidney failure. The United States Food and Drug Administration (FDA) published a public health advisory in June 2006 with updates in December 2006 and May 2007. A boxed warning for the gadolinium based contrast agents states that exposure to gadolinium based contrast agents increases the risk for NSF in patients with acute or chronic severe renal insufficiency.

Local Prevalence of Patients at Risk

In order to determine the number of at risk patients on a general medicine service, 110 admissions to the internal medicine ward service over a 1 year period were reviewed at the Veterans Affairs North Texas Healthcare System. If an estimated GFR (eGFR) less than 60 is the cutoff, the percentage of patients at risk is 32. If an eGFR of less than 30 is used, the percentage of patients at risk is 18. The percentage of at risk patients (eGFR less than 60) having magnetic resonance imaging exam (MRI) done at any time (performed at the VA North Texas Healthcare System) is 54. Forty one percent received gadolinium at least once. This data demonstrates that patients at risk for NSF are seen on a general medicine service and at risk patients have been administered gadolinium.

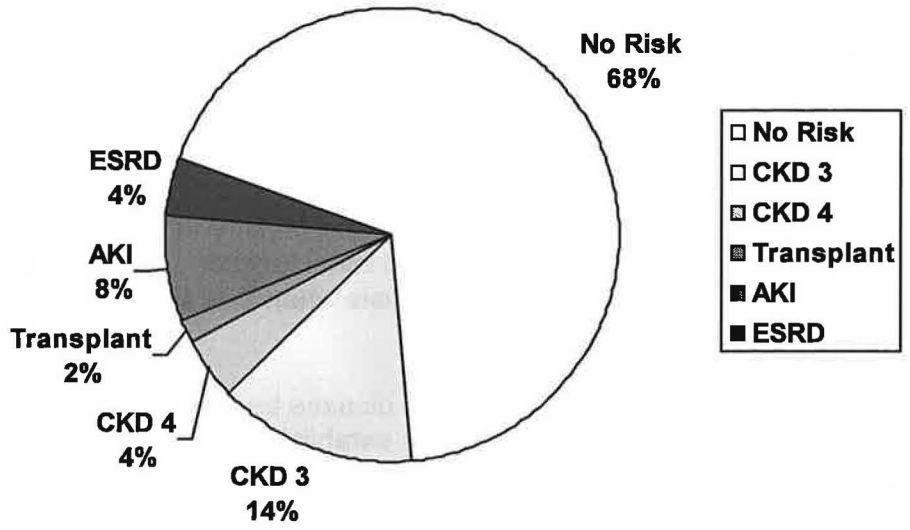


Figure 1: Patients at risk for NSF admitted to the VA North Texas Healthcare System. 110 admissions to the general internal medicine teaching service were reviewed over a 1 year period. All admissions were assigned to the same attending physician.

Clinical Findings

The age range is from 8 to 86 and there is no gender predilection.[6] Most cases develop within 6 months of an exposure to gadolinium, but there are reported cases of patients developing it after 1 year of exposure and there are two case reports of no known exposure to gadolinium. [7,8] All patients had a decreased renal function and 90 percent were on dialysis. Two cases with acute kidney injury (AKI) had an eGFR of over 30 ml/min/1.73m2. There is a disproportionate number of patients with Chronic Kidney Disease (CKD) Stage 4 who had a liver transplant or renal transplant.[9] The eGFR in these patients tends to overestimate the true GFR.[10,11] The true GFR in these patients may have been lower than reported.

The primary manifestations of NSF are skin changes and joint contractures; though autopsy studies in more severe cases have demonstrated that it is a systemic disease.[12-15] The skin is thickened and waxy with brawny hyperpigmentation or erythema. The persistent erythema has been mistaken for cellulitis.[6,16-20] There are plaques and subcutaneous nodules. Ninety seven percent of patients have involvement of the lower extremity, 77% have upper extremity involvement and 30% have involvement of the torso.[21] The head and neck are spared of skin changes. This helps differentiate NSF from scleromyxedema, a rare skin disorder that involves the head and neck and is

associated with paraproteinemia. Early reports described NSF as a scleromyxedema-like illness of renal disease.[22-25] Extra cutaneous involvement of head and neck include yellow scleral plaques of the eye[26] and fibrosis with stiffening of the jaw muscles.[27]

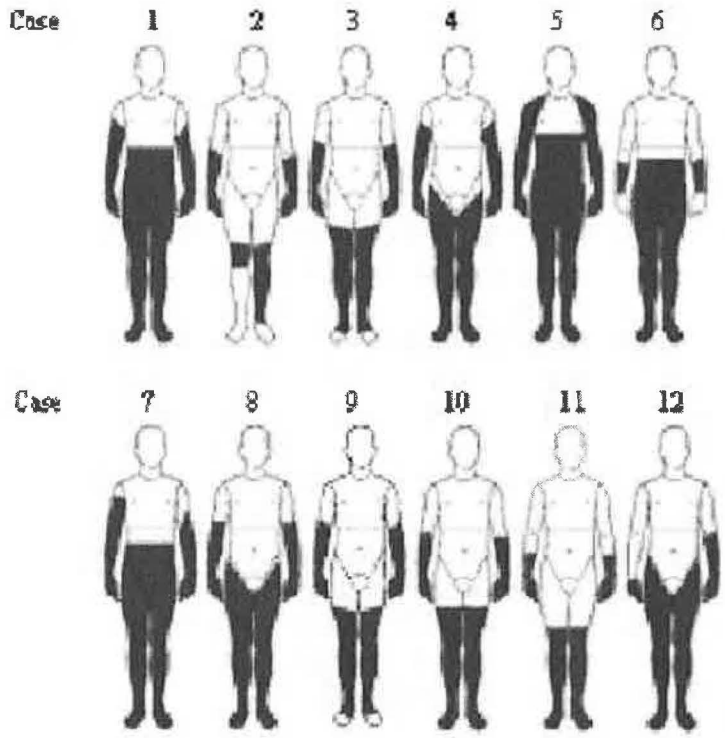


Figure:1 Distribution of NSF skin changes in 12 patients. The lower extremities are almost always affected and the head and neck are spared. Mendoza *et al.* Semin Arthritis Rheum, 2006.

Joint contractures were originally attributed to fibrosis and contractures of the skin, but later studies showed that fibrosis of the muscle and fascia contributed significantly to the contractures.[27] The joint itself is not involved. Joint contractures can lead to severe immobility leaving patients wheelchair bound and unable to do activities of daily living.[14] The contractures can also be extremely painful.[15]

Autopsy studies have shown extra-cutaneous involvement in many tissues. [12-15] The list is shown in table 1. One patient had involvement of the diaphragm. He eventually died from respiratory failure related to extensive fibrosis of the diaphragm with the inability to ventilate.[13] There is an increased risk of thrombosis manifested as deep venous thrombosis, pulmonary embolus, thrombosed arterio-venous access or atrial thrombus. Elevated antiphospholipid and anticardiolipin antibodies; deficient protein C, S, and antithrombin III levels; and presence of factor V Leiden were all observed in patients with NSF.[6,24,26,28,29]

NSF: Systemic Involvement	
Myocardium	Muscle
Pericardium	Bone
Lungs	Dura mater
Pleura	Kidney
Diaphragm	Testes

Table 1: Extra-cutaneous tissue involvement seen in autopsy cases

Histopathology

Skin biopsy reveals haphazardly arranged thickened dermal collagen bundles interspersed with increased numbers of plump fibroblasts with mucin deposition.[1,30] The fibrosis extends deeply into the subcutaneous tissue and muscle. A deep biopsy is needed to see this extension. The biopsy shows numerous fibrocytes recognized by positive staining for CD34 and procollagen-1 markers. Fibrocytes are circulating cells originating from the bone marrow. It has been speculated that the tissue reaction to gadolinium recruits circulating fibrocytes into the affected tissue.[18] Increased tissue levels of TGF beta are present in NSF biopsy samples[31] and TGF beta can cause fibrocytes to differentiate into a myofibroblast like cell that deposits collagen.[32] Similar histopathological changes are seen in extra-cutaneous tissues.[31] The histopathological findings are similar between NSF and scleromyxedema and require clinical correlation to differentiate between the two.[23] A list of diseases to consider in the differential diagnosis are listed in table 2.

NSF: Differential diagnosis	
Scleromyxedema	Porphyria cutanea tarda
Systemic sclerosis	Eosinophilic myalgia
Cellulitis	Eosinophilic fasciitis
Calciphylaxis	Spanish Toxic Oil syndrome
Amyloidosis	Fibroblastic rheumatism

Table 2: Differential diagnosis of NSF

Treatment

The treatments for NSF have not had much success. Many treatments have been tried and positive results are anecdotal case reports. The most reliable improvement comes with improvement in renal function in patients with acute kidney injury.[17] There are single case reports each for improvement with ultraviolet A1 and plasmapheresis. Both cases had an improvement in renal function after acute kidney injury and this may have been the reason for the improvement.[30,33] Extracorporeal photophoresis improved the skin distensibility in two dialysis patients and one patient with CKD who was not on dialysis. There

was no improvement in her serum creatinine over time.[34] Sodium thiosulfate (a treatment for calciphylaxis) improved the symptoms in an ESRD patient on chronic hemodialysis.[35] One peritoneal dialysis patient showed partial improvement in mobility after the first but not subsequent courses of intravenous immunoglobulin.[36]. A renal transplant recipient had improvement in pain with photodynamic therapy using methyl aminolaevulinate. There was no mention of the creatinine or GFR in the publication.[37] Physical therapy is used to prevent and treat joint contractures.

Gadolinium

There is no definitive treatment for NSF, therefore avoidance of the etiological agent is recommended. Administration of gadolinium (Gd) has been associated with NSF and details of Gd should be understood. Gd is an element in the Lanthanide series. It has an atomic number of 64 and a molecular weight of 157. Gd has unique elemental properties that make it a favorable contrast agent for magnetic resonance imaging. There are 7 unpaired electrons that give Gd a strong paramagnetic effect. A paramagnetic element will become magnetized when an external magnetic force is applied and, unlike ferromagnetic elements, a paramagnetic element will not retain its magnetism when the external magnetic force is removed. This property results in a disturbance of surrounding water protons when a magnetic field is applied during a MRI exam. This disturbance of relaxation is picked up as contrast on a MRI.

Free Gd, like other heavy metals is toxic. If given as $GdCl_3$ in rodents, the lethal dose in fifty percent of the rodents (LD50) is only 0.6 mmol/kg.[38] The FDA approved dose for a Gd enhanced MRI is 0.1 mmol/kg. The European Medicines Agency (EMEA) has approved a dose of 0.3 mmol/kg for magnetic resonance angiography with some Gd based contrast agents[39], though this dose and indication are not approved by the FDA. In practice, doses of up to 0.9 mmol/kg of Gd based contrast agents have been used as a replacement for x-ray angiography. [40] In order to deliver this dose of Gd, chelates with very strong binding affinities to Gd were developed. These chelates prevent the release of free Gd, yet still retain the ability to disturb the relaxation of surrounding water protons.

There are 5 Gd-chelates approved for use by the FDA and 8 approved for use by the EMEA. Gadoversetamide is the only chelate approved by the FDA that is not also approved by the EMEA. The chelates are listed in table 3. The properties of most of the chelates are similar. Molecular weights range from 559 to 1058. All are freely permeable across the glomerular basement membrane with no tubular secretion or reabsorption. None of the chelates are metabolized. Most of the chelates are distributed in the extracellular fluid and not taken up by cells or bound to protein. The excretion is similar to inulin or iothalamate and urinary excretion is equal to the glomerular filtration rate. The exceptions to these generalities include gadoxetic acid, gadofosveset, and gadobenate dimeglumine.

Gadoxetic acid is taken up by hepatocytes and 50% is excreted in the liver and 50% is excreted through the bile. It is marketed as a liver enhancing contrast agent. [41] Gadofosveset trisodium is 96% bound to albumin. This agent has been marketed as a blood pool agent because albumin binding keeps it in the circulation longer. [42] These two agents are not approved for use by the FDA. Gadobenate dimeglumine has minimal protein binding and is taken up by hepatocytes with a fecal excretion of four percent[43].

EMEA and FDA approved chelates								
Chelate	Trade Name Year-FDA	Chemical Structure	Charge	Dissociation half-life	M.W. Dalton	Half-life hours	% excreted 24 hr	NSF- Medwatch cases as of 1/17/07
Gadopentetate dimeglumine (Gd-DTPA)	Magnevist® 1988	Linear	Ionic	10 min	939	1.6±0.13	91±13	21
Gadoteridol (Gd-HP-DO3A)	ProHance® 1992	Cyclic	Non-ionic	3 hr	558.7	1.57±0.08	94.4±4.8	None
Gadodiamide (Gd-DTPA-BMA)	Omniscan® 1993	Linear	Non-ionic	30 sec	573.6	1.3±0.27	95.4±5.5	85
Gadobenate dimeglumine (Gd-BOPTA)	MultiHance® 2004	Linear	Ionic	NA	1058.2	1.17±0.26 2.02±0.60	NA	1- pt also received Omniscan
*Gadoversetamide (Gd-DTPA-BMEA)	OptiMARK® 1999	Linear	Non-ionic	NA	661.8	1.73±0.32	95.5±17.4	6
	Trade Name Year	Additional chelates approved by the EMEA						Reported cases
Gadobutrol (Gd-BT-DO3A)	Gadovist® 2001	Cyclic	Non-ionic	N/A	604	1.5	NA	None
Gadoterate meglumine (Gd-DOTA)	Dotarem® 1989	Cyclic	Ionic	N/A	559	1.5	90	None
Gadoxetic acid disodium salt (Gd-EOB-DTPA)	Primovist® 2004	Linear	Ionic	N/A	682	0.95	**>99%	None
Gadofosveset trisodium	Vasovist® 2005	Linear	Ionic	N/A	958	2-3	NA	None

Table3: Approved Gadolinium based contrast agents
*Gadoversetamide is approved for use by the FDA but not by the EMEA, though it is under review.
** Gadoxetic acid is excreted in both urine and feces.
Abbreviations: NSF, Nephrogenic systemic fibrsois; M.W., molecular weight; Yr-FDA, year the agent was FDA approved; EMEA, European Medicines Agency

Table 4: Studies showing gadolinium does not cause AKI

Author	Study	n	Agent	Dose (mmol/kg)	Renal Function	Result	Prevention
Rofsky 1991[12]	Renal mass workup Mean age 69	5	Magnevist®	0.1	[Cr] >2.0 mg/dL Range 2.2-6.0	No increase [Cr]	NA
Bellin 1992[7]	Prospective consecutive pts 10 IV Gd 10 no contrast	20	Dotarem®	0.1	C-G <60 ml/min mean GFR 21.1± 3.2	No [Cr] ↑ >25% [Cr] ↑ >10% in 5 controls and 3 Gd pts	None
Prince 1996[10]	Retrospective IC vs Gd-chelate	64	Magnevist®-21 Omniscan®-37 ProHance®- 6	0.2-0.4	[Cr] >1.5 mg/dL	IC- 9/31 29% Gd- 0% CIN ≥0.5 mg/dL	NA
Kaufman 1999[9]	Digital subtraction vena cavogram Mean age 66.7	14	Omniscan® Magnevist®	≤0.4	[Cr] ≥1.5 mg/dL mean 2.8±1.1	3 pts [Cr] ↑ due to other causes CIN ≥0.5 mg/dL-48 hr	NA
Spinosa 1999[15]	Mean age 59 Renal arteriogram	25	Omniscan®	<0.3	[Cr] >1.5 mg/dL mean 3.1	2 pts-[Cr] ↑ due to other causes CIN >0.5 mg/dL-48 hr	Hydration
Hammer 1999[8]	DSA arterial Mean age 53.1	34	Magnevist®	0.4	[Cr] >1.5 mg/dL	CIN- 1/34 CIN- >0.5 mg/dL	NA
Spinosa 2000[14]	15- IC and CO_2 20- Gd and CO_2 7-CO_2 alone	42	Omniscan®	up to 0.4	[Cr] >1.5 mg/dL mean 2.2 range 1.6-3.6	IC- 6/15 40% Gd- 1/20 5% CIN ≥0.5 mg/dL	300-500 ml NS pre
Townsend 2000[16]	Prospective Infusion only No imaging done	32	Omniscan® vs NS	0.2	CrCl 20-29 ml/min, n-9 CrCl 30-60, n-11	No CIN CIN- >0.5 mg/dL	NS after bolus
Sancak 2002[13]	Mean age 53 UE or SVC venography	16	Omniscan®	0.3	Mean [Cr] 1.5 mg/dL range 1.2-1.8	Largest ↑ in [Cr] 0.2 mg/dL	NA
Rieger 2002[11]	Prospective procedures (arterial and IV)	32	Magnevist®	0.34± 0.06	[Cr] >1.5 mg/dL Mean 3.6±1.4	1 pt-[Cr] ↑ due to cholesterol emboli CIN >0.5 mg/dL-72 hr	All received some NS

Abbreviations: AKI, acute kidney injury; Cr, creatinine; DSA, digital subtraction angiography; LE, lower extremity; pts, patients; IV, intravenous; IC, iodinated contrast; UE, upper extremity; SVC, superior vena cava; CIN, contrast induced nephropathy; Gd, gadolinium; NS, normal saline; NA, not available; CrCl, creatinine clearance

Nephrotoxicity of Gd-chelates

MRI/MRA with Gd enhancement is often used in patients with renal insufficiency in order to avoid the nephrotoxicity of iodinated contrast. Gd-chelates have also been used to replace iodinated contrast in x-ray angiography in patients with CKD. Early studies showed demonstrated a low risk of acute kidney injury with. Table two summarizes these studies.[44-53] Limitations of these reports include: small sample size; many lacked control groups; little uniformity of pretreatment regimens; variable Gd doses and routes of administration; and variable definitions of contrast-induced nephropathy (CIN). Because of these early studies

the dose of Gd-chelates increased over time with the thought that Gd-chelates were safe in patients with renal insufficiency.

Later studies began to demonstrate that Gd-chelates did in fact cause nephrotoxicity in patients with CKD.[54-57] These studies contained more patients, one was prospective, and doses employed were on average higher than earlier series. There is one case of biopsy proven acute tubular necrosis in a patient with acute kidney injury following a Gd-chelate dose.[58] There is one case report where a patient with CKD received iodinated contrast for coronary angiography with no nephrotoxicity. Three years later he developed acute kidney injury after only 0.14 mmol/kg of gadodiamide for a MRA study indicating that gadolinium could be more nephrotoxic than iodinated contrast even at doses less than 0.2 mmol/kg.[59] A position paper from the Contrast Media Safety Committee of the European Society of Urogenital Radiology in 2000 recommended gadolinium-chelates should not replace iodinated contrast media in patients with CKD for radiographic examinations based on nephrotoxicity data.[60]

Table 5: Studies showing gadolinium is nephrotoxic

Author	Study	n	Agent	Dose (mmol/kg)	Renal function	Result	Prevention
Sam 2003[20]	Retrospective CKD 1/99-1/01 No control	195	Magnevist®- 195	0.28	*CrCl <80 ml/min by CG* Mean 38.2±16	CIN- 7/195 (3.5%) MRA- 3/153 (1.9%) DSA- 4/42 (9.5%) CIN >1.0 mg/dL- 48 hr with oligoanuria	NA
Erley 2004[19]	Prospective Randomized	21	Gadovist®- 10 vs Iohexol-11	0.57±0.17	[Cr] >1.5 mg/dL or *GFR <50 ml/min	CIN: - 50% Gadovist - 45% Iohexol CIN- >50% decrease in GFR	IV hydration
Briguori 2006[17]	Retrospective consecutive pts Historical controls, Coronary procedures	25	Omniscan®-8 Gadovist®-17 3 parts Gd-chelate was mixed with 1part IC vs IC alone	0.6±0.3 0.28-1.23	[Cr] >2 mg/dL or CrCl <40 ml/min	CIN: Gd & IC- 7/25 (28%) IC alone- 2/32 (6.5%) CIN ≥0.5 mg/dL within 48 h or dialysis within 5 days	NS plus NAC
Ergun 2006[18]	Retrospective 2/99-3/05 No controls [Cr] pre, days 1,3,7, & 1 month	91	Magnevist® Omniscan® Dotarem®	0.2	Stage 3 and 4 CKD *Mean eGFR- 33 (15-58) ml/min/1.73m^2	CIN- 11/91 (12/1%) CIN ≥0.5 mg/dL within 72 h	NA

Abbreviations: CKD, chronic kidney disease; pts, patients; Gd, gadolinium; IC, iodinated contrast; CG, Cockcroft Gault; eGFR, estimated glomerular filtration rate; CIN, contrast induced nephropathy; MRA, magnetic resonance imaging; DSA, digital subtraction angiography; GFR, glomerular filtration rate; IV, intravenous; NS, normal saline; NAC, N-acetylcysteine.

Deposition of Gd in tissue

Gadolinium has been shown to deposit in the bone of patients with a normal GFR. Bone fragments were analyzed in patients undergoing a hip replacement. Gd levels were not detected in patients who did not receive a Gd-chelate prior to the hip replacement. Subjects who received gadodiamide (a linear Gd-chelate) had higher levels in the bone (1.77 vs. 0.477 µg Gd/gm bone) than those who received the gadoteridol (a cyclic Gd-chelate). The cyclic chelate was hypothesized to have a more stable binding than the linear chelate.[61,62]

In patients with NSF, Gd levels were identified and then measured in skin biopsy specimens of affected skin samples. Four of seven patients had Gd in their NSF affected skin samples. The Gd levels were 70 µg Gd/gm tissue in NSF affected skin. A sample of skin from a patient with NSF was taken for actinic keratosis and did not have features of NSF. The level of Gd in this sample was much lower at 5 µg Gd/gm tissue indicating that the higher levels of Gd seen in the affected skin samples was responsible for NSF.

Link to Gadolinium

After the initial link was made with Gd by Grobner, several more reports appeared documenting the association of Gd with NSF. Each publication has details that have shaped the recommendations regarding the use of gadolinium compounds.

Deo *et al.* compared three patients with NSF to patients in a dialysis practice in Connecticut. Two of the NSF affected patients received gadodiamide and 1 patient received gadopentetate dimeglumine. The incidence of NSF was 4.2 per 1000 patient years. The risk of developing NSF was determined to be 2.4% per Gd exposure. [63] This study emphasized that the incidence in a dialysis population was low, but the risk for NSF was high if exposed to gadolinium.

The Centers for Disease Control and Prevention (CDC) published NSF associations in their Morbidity and Mortality Weekly Report. Thirty three cases of NSF were associated with the administration of a Gd-chelate. Nineteen of these patients were studied in more detail. The type of contrast was not mentioned in the report. The attack rate for NSF was 0.61 per 100 hemodialysis patients. The attack rate for peritoneal dialysis patients was much higher at 4.6 per 100 patients. The only statistically significant factor in a multivariate analysis was exposure to a Gd-chelate within 12 months with an odds ratio of 8.97. Four patients were exposed to Gd more than 1 year prior to the onset of NSF and 1 patient had no known Gd exposure. [7] The study demonstrates that peritoneal dialysis patients have an increased risk of developing NSF over hemodialysis patients. It is only one of two reported cases in the literature of a patient with NSF that did not have a known exposure to Gd.[8]

Khurana *et al.* reviewed 6 cases of NSF related to gadodiamide exposure. Five of these patients were not on dialysis at the time of exposure to gadodiamide and one had ESRD and was on dialysis. The five patients without end stage renal disease (ESRD) included two with CKD stage 5, 2 with failed transplants and 1 with AKI. All 5 of these patients received dialysis after the gadolinium exposure. The patient with AKI eventually recovered renal function and had only mild improvement in his skin disease.[64] This publication demonstrates that Gd can cause NSF in patients who are not on dialysis.

In a series by Sadowski *et al.*, 13 patients with NSF received gadodiamide and one patient received both gadodiamide and gadobenate dimeglumine. These 13 subjects were compared to 4,236 patients who had received a Gd-chelate, but did not develop NSF. Affected patients had higher serum creatinine levels, a greater number of Gd-enhanced MRI exams and more pro inflammatory events such as thromboembolic events, surgery, or infections. [65] This study emphasized the contribution of pro-inflammatory events seen in earlier studies.[16,24,26,66]

Broome *et al.* reported 12 patients with NSF after gadodiamide exposure. 168 dialysis patients had 559 MRI exams. 12 patients who developed NSF out of 301 gadodiamide exposures were compared to 258 MRI exams without gadodiamide exposure. Four of the twelve patients were liver transplant recipients with AKI from hepatorenal syndrome. Odds ratio for exposure was again high at 22.3 and NSF prevalence in gadodiamide-exposed dialysis patients was 4.0%. A dose of 0.1 mmol/kg was compared to 0.2 mmol/kg and the odds ratio with the higher dose was 12.1, suggesting that the risk of developing NSF is dose dependent. Daily dialysis for 3 days after Gd administration did not prevent NSF in four patients with AKI secondary to hepatorenal syndrome.[9]

Marckman, *et al.* initially reviewed 13 cases of NSF in Denmark. The odds ratio for exposure was 32.5 compared to ESRD patients with no exposure to a Gd-chelate. [67] No new cases of NSF have developed since the use of gadodiamide has been discontinued. [68] A review of 19 cases of gadodiamide induced NFS were reviewed for significant cofactors. The primary risk for NSF was an increasing cumulative dose of gadodiamide. There was also a significant association with elevated serum calcium and phosphorus levels and the dose of epoetin beta but no correlation with serum PTH levels, acidosis or angiotensin converting enzyme use. [69] This is the first study that looked at cofactors for gadodiamide induced NSF.

The total number of cases reported in the literature associating the use of Gd-chelates to NSF is 96. Sixty three cases have an identified chelate. Sixty two cases are associated with gadodiamide. One patient received both gadodiamide and gadopentetate dimeglumine and one patient received only gadopentetate. The number of cases reported to the FDA through MedWatch is 112. MedWatch reports are volunteer reports that do not require peer review and most likely have

overlap with the published case reports. Eighty five cases were associated with gadodiamide, 21 with gadopentetate dimeglumine and 6 with gadoversetamide. The last FDA update in May, 2003 reports cases of NSF occurring after sequential administration of gadodiamide with gadobenate dimeglumine and gadodiamide with gadoteridol.[70] Gadopentetate dimeglumine and gadodiamide lead the Unites States market in sales of GD-chelates. There are no reported cases of NSF for the non FDA approved chelates that are available for use in Europe.

Structure and Gd dissociation

The proposed mechanism for NSF is excess Gd deposition. The decreased clearance of these Gd-chelates in patients with decreased renal function makes the chance of dechelation more likely. The structure of the chelates may play a role in this enhanced dechelation. Thermodynamic stability, transmetalation and kinetic stability are properties related to the structure of the chelates.

Thermodynamic stability for the Gd-chelates is defined by the equation: [Gd-chelate]/[Gd][chelate]. The log of the thermodynamic constants is listed in table 6. Cyclic chelates have higher binding affinities than the linear chelates.

Table 6: Taken from Prince et al. Radiology 2003; 227(3) 639-46.

Factors Related to Binding of Gadolinium to Different Chelates and to Chelate Elimination

	Linear Chelate			Macrocyclic Chelate	
Factor	Gadodiamide*	Gadoversetamide†	Gadopentatate Dimeglumine‡	Gadoterate Meglumine§	Gadoteridol‖
Stability constant (log base 10)#	16.9	16.6	22.1	25.8	23.8
Conditional stability constant at pH 7.4#	14.9	15.0	18.1	18.8	17.1
Dissociation half-life#	30 sec	Not available	10 min	>1 mo	3 h
Distribution half-life (min)**	3.7 ± 2.7	13.3 ± 6.8	14.4 ± 8.4	7.1 ± 9.2	12 ± 2.4
Volume of distribution (mL/kg) **	200 ± 61	162 ± 25	266 ± 43	171 ± 20	204 ± 58
Elimination half-life (min)**	77.8 ± 16	103.6 ± 19.5	94 ± 11	91 ± 14	94.2 ± 4.8
Renal/plasma clearance (mL/min/kg)	1.7/1.8	1.15/1.20	1.76/1.94	Not available	1.4/1.5

* Source: references 12 and 13.
† Source: references 10 and 14.
‡ Source: references 11 and 12.
§ Source: references 12 and 15.
‖ Source: references 12 and 16.
These values may be different in highly acidic or basic conditions of colorimetric assays.
** Mean values ± SDs.

Transmetallation for Gd-chelates is defined by the following reaction: Gd-chelate + Zn → free Gd + Zn-chelate. Zinc has high enough binding affinity and concentration in the serum to cause clinically significant transmetalation. Urinary Zinc excretion has been used to measure the transmetalation of various Gd-chelates. However, some of the commercial Gd-chelates have excess chelate in order to prolong the shelf life which makes urinary Zinc excretion unreliable.[71] However, in vitro transmetalation experiments demonstrate that the linear chelates (gadodiamide and gadopentetate dimeglumine) are more likely to release free Gd than a cyclic chelate (gadoteridol).[72]

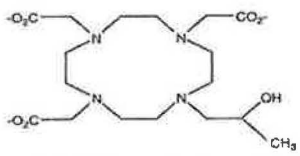
Kinetic stability is related again to the structure and probably plays the most important role in determining the release of free Gd in patients with decreased renal function. While the thermodynamic stability relates to the dissociation achieved at equilibrium, the kinetic stability determines the rate at which it reaches this equilibrium. In patients with normal GFR, the rapid clearance prevents the Gd-chelates from reaching equilibrium. In patients with decreased renal function, the prolonged time in circulation allows more time for the Gd-chelates to dissociate. Kinetic stability can be expressed as T1/2 which is the dissociation half-life. The linear chelates bind Gd in a flexible line. The bonds can be broken sequentially resulting in less kinetic stability. The cyclic Gd-chelates have a rigid ring that binds Gd. Gd has to break all bonds simultaneously to be released. This results in an improved kinetic stability and a shorter dissociation half-life.[72,73] In addition to structure, the charge also plays a role in kinetic stability. Gd has three positive charges. Chelates with more than three negative charges are ionic because after binding Gd they have a negative charge. Ionic chelates have more kinetic stability than non ionic chelates.

A list of chelates in order of their ability to dissociate is shown in table 5. Gadodiamide is a non-ionic cyclic chelate with the one of the lowest thermodynamic stability constants and a high transmetalation potential. It has the most reported cases of NSF in the literature. Gadoversetamide is also a non-ionic cyclic chelate with a low thermodynamic stability and high transmetalation potential. There are not as many cases associated with NSF in the literature, but this maybe related to a lower market share. Gadoteridol is a non-ionic cyclic chelate. There is only one reported cases associated with NSF, but it was given sequentially with gadodiamide. It may carry the least risk of causing NSF of the available chelates in the United States.

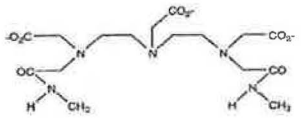
Table 7: Gd-chelates listed in order of risk for NSF. Taken from the MHRA public assessment report, February 2007.

Brand name	Generic name	Acronym	Chemical structure	Charge	Cases of NSF
Omniscan	gadodiamide	Gd-DTPA-BMA	Linear	Non-ionic	Yes
OptiMARK*	gadoversetamide	Gd-DTPA-BMEA	Linear	Non-ionic	Yes
Magnevist	gadopentetate dimeglumine	Gd-DTPA	Linear	Ionic	Yes
MultiHance	gadobenate dimeglumine	Gd-BOPTA	Linear	Ionic	No
Primovist	gadoxetic acid disodium salt	Gd-EOB-DTPA	Linear	Ionic	No
Vasovist	gadofosveset trisodium	Gd-DTPA	Linear	Ionic	No
ProHance	gadoteridol	Gd-HP-DO3A	Cyclic	Non-ionic	No
Gadovist	gadobutrol	Gd-BT-DO3A	Cyclic	Non-ionic	No
Dotarem	gadoterate meglumine	Gd-DOTA	Cyclic	Ionic	No

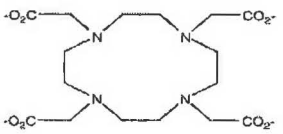
Figure 2: Structure and charge of different chelates



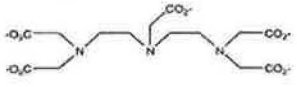
gadoteridol: nonionic cyclic



gadodiamide: nonionic linear



gadoterate meglumine: ionic cyclate



gadopentetate dimeglumine: ionic Linear

Figure 3: FDA Boxed Warning from the May23, 2007 update.

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/1.73m^2), 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.

Recommendations

The FDA[70], Danish Medicines Association (DMA)[5] , United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA)[74], and American College of Radiology (ACR)[75], among others have published recommendations regarding gadolinium use. The recommendations from these agencies were chosen in order to discuss some of the more controversial recommendations. The MHRA was a public assessment report to the European Medicines Agency (EMEA) but does not represent the view of all member states. The DMA report is an independent Danish report. The ACR recommendations were derived from a blue ribbon panel and represent the consensus of the members, but have not been adapted as policy.[80]

The FDA has is the only agency that has not stated that gadodiamide is contraindicated in patients at risk for NSF. The FDA does mention that gadodiamide has the highest incidence of reported associations with NSF, but states that all FDA approved Gd-chelates have been associated with NSF and should be used with caution. The FDA warnings in June and December 2006 stated that patients with a GFR of less than 60ml/min/1.73m^2 were at risk. The latest update in May changed the GFR to less than 30ml/min/1.73m^2 but stated that patients with any degree of acute renal insufficiency due to the hepatorenal syndrome or in the perioperative liver transplant period were at increased risk. The DMA and MHRA state that gadodiamide is contraindicated in patients with a GFR of less than 30ml/min/1.73m^2. The ACR and Kuo et al. state that gadodiamide is contraindicated in any patient with any degree of renal disease.[76] The ACR and MHRA state that gadopentetate dimeglumine and gadoversetamide have an increased risk for NSF but there are no recommendations to avoid these chelates.

The MHRA recommends that a serum creatinine should be obtained before a patient receives a Gd-chelate. The FDA recommends that patients should be evaluated for renal disease with either a medical history or laboratory tests that measure renal function. The ACR specifically states that a creatinine is not necessary and instead recommends screening for renal disease with information provided by the referring physician or from a patient questionnaire.

All groups recommend that approved doses should not be exceeded. But since the maximum dose approved by the FDA is only 0.1 mmol/kg and use as an MRA agent is not approved, this would eliminate the use of MRA exams in the United States. This also would eliminate the use of Gd-chelates as a replacement for x-ray angiography since this use and the doses required are not approved by either the EMEA or the FDA. This latter use was typically used in patients with decreased renal function to prevent contrast induced nephropathy from iodinated contrast. Recent data has shown that Gd-chelates are nephrotoxic, particularly at the dose used in x-ray angiography.[55-57,77] The use of Gd-chelates with x-ray angiography should therefore have few indications.

The FDA and ACR recommend considering prompt dialysis after a patient has been given a dose of Gd based on studies showing that Gd disappears from the blood with hemodialysis. Three standard hemodialysis sessions will remove 98.9% of a 0.1mmol/kg dose of gadodiamide.[78] However, three daily dialysis sessions after a dose of gadodiamide did not prevent NSF in 4 patients with AKI.[9] The FDA points this out in its FDA warning but still recommends considering prompt dialysis for patients already on dialysis. The original FDA warning recommended considering hemodialysis even in patients with decreased renal function not yet on dialysis. This latter recommendation was removed from the latest update in May, 2007. Prompt dialysis in a patient already on dialysis with a functioning access is reasonable. However, dialysis should not be considered as a way to decrease the risk so the procedure can be done safely. In contrast, the patients at highest risk are patients with ESRD even if dialysis is performed promptly. As all agencies state, the need for a Gd enhanced MRI exam should only be done if the diagnostic information is essential and cannot be obtained with alternative imaging.

The patients at highest risk for NSF are peritoneal dialysis patients.[7] Only 69% of Gd is removed after 22 days in patients treated with peritoneal dialysis.[79] If a Gd enhanced MRI is essential, a peritoneal dialysis patient should be treated with hemodialysis to help clear the gadolinium. But once again, hemodialysis should not be used as a means to make the administration of Gd safe.

Other recommendations include avoiding multiple doses since the risk of NSF increases with cumulative doses. If multiple doses are required, the FDA recommends allowing sufficient time for the Gd-chelate to be eliminated before administering the next dose. This would be 3-4 dialysis treatments in a patient

on hemodialysis. In patients with CKD stage five the half-life is extended to 34 hours.[79] To eliminate 95% of the Gd-chelate would take approximately 1 week. In patients with AKI Gd-chelates should be avoided until the renal function improves. Liver transplant recipients and patients with hepatorenal syndrome are at increased risk even with only moderate renal insufficiency and Gd-chelates should be avoided in these patients.

Conclusion:

NSF is a rare disorder seen only in patients with renal insufficiency. An association has been made with Gd based contrast agents in patients with a decreased renal function. The main manifestations are skin changes and joint contractures. Deaths directly attributable to NSF are rare, but severely disabling contractures are common. The proposed mechanism is deposition of free Gd in tissues with a subsequent fibrotic reaction. Treatment has not had much success and avoidance of Gd in these patients is the key to prevention. Some of the Gd-chelates appear to carry more of a risk than others and should be avoided in patients with any renal dysfunction.

References

1. Cowper SE *et al.* (2000) Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* **356:** 1000-1001
2. Daram SR *et al.* (2005) Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis: report of a new case with literature review. *Am J Kidney Dis* **46:** 754-759
3. Cowper SE *et al.* (2006) Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis--setting the record straight. *Semin Arthritis Rheum* **35:** 208-210
4. Grobner T (2006) Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* **21:** 1104-1108
5. Danish Medicines Agency. (May 2006) Investigation of the safety of MRI contrast medium Omniscan [press release]. Copenhagen: Danish Medicines Agency; 29.
6. Jain SM *et al.* (2004) Nephrogenic fibrosing dermopathy in pediatric patients. *Pediatr Nephrol* **19:** 467-470
7. Centers for Disease Control and Prevention. (2007) Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents--St. Louis, Missouri, 2002-2006. *MMWR* **56**:137-141.
8. Weiss AS *et al.* (2007) A case of nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis. *Nat Clin Pract Nephrol* **3:** 111-115
9. Broome DR *et al.* (2007) Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR Am J Roentgenol* **188:** 586-592
10. Poge U *et al.* (2005) MDRD equations for estimation of GFR in renal transplant recipients. *Am J Transplant* **5:** 1306-1311
11. Cantarovich M *et al.* (2006) Poor prediction of the glomerular filtration rate using current formulas in de novo liver transplant patients. *Transplantation* **82:** 433-436
12. Gibson SE *et al.* (2006) Multiorgan involvement in nephrogenic fibrosing dermopathy: an autopsy case and review of the literature. *Arch Pathol Lab Med* **130:** 209-212
13. Kucher C *et al.* (2006) Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis with diaphragmatic involvement in a patient with respiratory failure. *J Am Acad Dermatol* **54:** S31-34
14. Ting WW *et al.* (2003) Nephrogenic fibrosing dermopathy with systemic involvement. *Arch Dermatol* **139:** 903-906
15. Krous H *et al.* (2007) Nephrogenic Systemic Fibrosis with Multiorgan Involvement in a Teenage Male after Lymphoma, Ewing Sarcoma, End Stage Renal Disease, and Hemodialysis. *Pediatr Dev Pathol*: 1
16. Cowper SE (2003) Nephrogenic fibrosing dermopathy: the first 6 years. *Curr Opin Rheumatol* **15:** 785-790
17. Cowper SE *et al.* (2001) Nephrogenic fibrosing dermopathy. *Am J Dermatopathol* **23:** 383-393
18. Galan A *et al.* (2006) Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). *Curr Opin Rheumatol* **18:** 614-617

19. George DE *et al.* (2006) Nephrogenic fibrosing dermopathy: case report and review. *Dermatol Online J* **12:** 7
20. Lewis KG *et al.* (2006) Nephrogenic fibrosing dermopathy and calciphylaxis with pseudoxanthoma elasticum-like changes. *J Cutan Pathol* **33:** 695-700
21. Mendoza FA *et al.* (2006) Description of 12 cases of nephrogenic fibrosing dermopathy and review of the literature. *Semin Arthritis Rheum* **35:** 238-249
22. Neudecker BA *et al.* (2005) Scleromyxedema-like lesions of patients in renal failure contain hyaluronan: a possible pathophysiological mechanism. *J Cutan Pathol* **32:** 612-615
23. Kucher C *et al.* (2005) Histopathologic comparison of nephrogenic fibrosing dermopathy and scleromyxedema. *J Cutan Pathol* **32:** 484-490
24. Mackay-Wiggan JM *et al.* (2003) Nephrogenic fibrosing dermopathy (scleromyxedema-like illness of renal disease). *J Am Acad Dermatol* **48:** 55-60
25. McNeill AM and Barr RJ (2002) Scleromyxedema-like fibromucinosis in a patient undergoing hemodialysis. *Int J Dermatol* **41:** 364-367
26. Streams BN *et al.* (2003) Clinical and pathologic features of nephrogenic fibrosing dermopathy: a report of two cases. *J Am Acad Dermatol* **48:** 42-47
27. Levine JM *et al.* (2004) Involvement of skeletal muscle in dialysis-associated systemic fibrosis (nephrogenic fibrosing dermopathy). *Muscle Nerve* **30:** 569-577
28. Hubbard V *et al.* (2003) Scleromyxoedema-like changes in four renal dialysis patients. *Br J Dermatol* **148:** 563-568
29. Swartz RD *et al.* (2003) Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure. *Am J Med* **114:** 563-572
30. Baron PW *et al.* (2003) Nephrogenic fibrosing dermopathy after liver transplantation successfully treated with plasmapheresis. *Am J Dermatopathol* **25:** 204-209
31. Jimenez SA *et al.* (2004) Dialysis-associated systemic fibrosis (nephrogenic fibrosing dermopathy): study of inflammatory cells and transforming growth factor beta1 expression in affected skin. *Arthritis Rheum* **50:** 2660-2666
32. Abe R *et al.* (2001) Peripheral blood fibrocytes: differentiation pathway and migration to wound sites. *J Immunol* **166:** 7556-7562
33. Kafi R *et al.* (2004) UV-A1 phototherapy improves nephrogenic fibrosing dermopathy. *Arch Dermatol* **140:** 1322-1324
34. Gilliet M *et al.* (2005) Successful treatment of three cases of nephrogenic fibrosing dermopathy with extracorporeal photopheresis. *Br J Dermatol* **152:** 531-536
35. Yerram P *et al.* (2007) Nephrogenic Systemic Fibrosis: A Mysterious Disease in Patients with Renal Failure--Role of Gadolinium-Based Contrast Media in Causation and the Beneficial Effect of Intravenous Sodium Thiosulfate. *Clin J Am Soc Nephrol* **2:** 258-263
36. Chung HJ and Chung KY (2004) Nephrogenic fibrosing dermopathy: response to high-dose intravenous immunoglobulin. *Br J Dermatol* **150:** 596-597
37. Schmook T *et al.* (2005) Successful treatment of nephrogenic fibrosing dermopathy in a kidney transplant recipient with photodynamic therapy. *Nephrol Dial Transplant* **20:** 220-222

38. Caille JM *et al.* (1983) Gadolinium as a contrast agent for NMR. *AJNR Am J Neuroradiol* **4:** 1041-1042
39. Bellin MF (2006) MR contrast agents, the old and the new. *Eur J Radiol* **60:** 314-323
40. Morcos SK *et al.* (1999) Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol* **9:** 1602-1613
41. Hamm B *et al.* (1995) Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. *Radiology* **195:** 785-792
42. Lauffer RB *et al.* (1998) MS-325: albumin-targeted contrast agent for MR angiography. *Radiology* **207:** 529-538
43. Kirchin MA *et al.* (1998) Gadobenate dimeglumine (Gd-BOPTA). An overview. *Invest Radiol* **33:** 798-809
44. Bellin MF *et al.* (1992) Gd-DOTA: evaluation of its renal tolerance in patients with chronic renal failure. *Magn Reson Imaging* **10:** 115-118
45. Hammer FD *et al.* (1999) Gadolinium dimeglumine: an alternative contrast agent for digital subtraction angiography. *Eur Radiol* **9:** 128-136
46. Kaufman JA *et al.* (1999) Gadolinium-based contrast agents as an alternative at vena cavography in patients with renal insufficiency--early experience. *Radiology* **212:** 280-284
47. Prince MR *et al.* (1996) Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. *J Magn Reson Imaging* **6:** 162-166
48. Rieger J *et al.* (2002) Gadolinium as an alternative contrast agent for diagnostic and interventional angiographic procedures in patients with impaired renal function. *Nephrol Dial Transplant* **17:** 824-828
49. Rofsky NM *et al.* (1991) Renal lesion characterization with gadolinium-enhanced MR imaging: efficacy and safety in patients with renal insufficiency. *Radiology* **180:** 85-89
50. Sancak T *et al.* (2002) Gadodiamide as an alternative contrast agent in intravenous digital subtraction angiography and interventional procedures of the upper extremity veins. *Cardiovasc Intervent Radiol* **25:** 49-52
51. Spinosa DJ *et al.* (2000) Lower extremity arteriography with use of iodinated contrast material or gadodiamide to supplement CO2 angiography in patients with renal insufficiency. *J Vasc Interv Radiol* **11:** 35-43
52. Spinosa DJ *et al.* (1999) Renal insufficiency: usefulness of gadodiamide-enhanced renal angiography to supplement CO2-enhanced renal angiography for diagnosis and percutaneous treatment. *Radiology* **210:** 663-672
53. Townsend RR *et al.* (2000) Safety of intravenous gadolinium (Gd-BOPTA) infusion in patients with renal insufficiency. *Am J Kidney Dis* **36:** 1207-1212
54. Briguori C (2006) Gadolinium-based contrast agents and nephrotoxicity in patients undergoing coronary artery procedures. *Catheter Cardiovasc Interv* **68:** 813
55. Ergun I *et al.* (2006) The safety of gadolinium in patients with stage 3 and 4 renal failure. *Nephrol Dial Transplant* **21:** 697-700

56. Erley CM *et al.* (2004) Gadolinium-based contrast media compared with iodinated media for digital subtraction angiography in azotaemic patients. *Nephrol Dial Transplant* **19:** 2526-2531
57. Sam AD *et al.* (2003) Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. *J Vasc Surg* **38:** 313-318
58. Akgun H *et al.* (2006) Are gadolinium-based contrast media nephrotoxic? A renal biopsy study. *Arch Pathol Lab Med* **130:** 1354-1357
59. Thomsen HS (2004) Gadolinium-based contrast media may be nephrotoxic even at approved doses. *Eur Radiol* **14:** 1654-1656
60. Thomsen HS *et al.* (2002) Gadolinium-containing contrast media for radiographic examinations: a position paper. *Eur Radiol* **12:** 2600-2605
61. Gibby WA *et al.* (2004) Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy. *Invest Radiol* **39:** 138-142
62. White GW *et al.* (2006) Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol* **41:** 272-278
63. Deo A *et al.* (2007) Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. *Clin J Am Soc Nephrol* **2:** 264-267
64. Khurana A *et al.* (2007) Nephrogenic systemic fibrosis: a review of 6 cases temporally related to gadodiamide injection (omniscan). *Invest Radiol* **42:** 139-145
65. Sadowski EA *et al.* (2007) Nephrogenic Systemic Fibrosis: Risk Factors and Incidence Estimation. *Radiology*
66. Maloo M *et al.* (2006) Nephrogenic systemic fibrosis among liver transplant recipients: a single institution experience and topic update. *Am J Transplant* **6:** 2212-2217
67. Marckmann P *et al.* (2006) Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* **17:** 2359-2362
68. Thomsen HS *et al.* (2007) Enhanced Computed Tomography or Magnetic Resonance Imaging: A Choice between Contrast Medium-Induced Nephropathy and Nephrogenic Systemic Fibrosis? *Acta Radiol* **48:** 593-596
69. Marckmann P *et al.* (2007) Case-control study of gadodiamide-related nephrogenic systemic fibrosis. *Nephrol Dial Transplant*
70. U.S. Food and Drug Administration. (2007) Information for healthcare professionals: gadolinium-containing contrast agents for magnetic resonance imaging (MRI) (marketed as Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance). Rockville, MD: U.S. Food and Drug Administration; 6/2006, updated 12/2006 and 5/2007.
71. Prince MR *et al.* (2003) Gadodiamide administration causes spurious hypocalcemia. *Radiology* **227:** 639-646
72. Idee JM *et al.* (2006) Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fundamental & clinical pharmacology* **20:** 563-576

73. Tweedle MF (1992) Physicochemical properties of gadoteridol and other magnetic resonance contrast agents. *Invest Radiol* **27 Suppl 1:** S2-6
74. MHRA (February 2007) Public Assessment Report - Increased risk of nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis and gadolinium-containing MRI contrast agents.
75. Kanal E *et al.* (2007) ACR guidance document for safe MR practices: 2007. *AJR AM J Roentgenol* **188**: 1447-1474.
76. Kuo PH *et al.* (2007) Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology* **242:** 647-649
77. Briguori C *et al.* (2006) Gadolinium-based contrast agents and nephrotoxicity in patients undergoing coronary artery procedures. *Catheter Cardiovasc Interv* **67:** 175-180
78. Saitoh T *et al.* (2006) Dialyzability of gadodiamide in hemodialysis patients. *Radiat Med* **24:** 445-451
79. Joffe P *et al.* (1998) Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acad Radiol* **5:** 491-502
80. Van Moore A, Jr. (2007) Commentary on "ACR guidance document for safe practices: 2007". *AJR AM J Roentgenol* **188**: 1446