# Current Status of Gadolinium Toxicity in Patients with Kidney Disease

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**Gadolinium-based contrast (GBC) agents have recently been the subject of intense interest for physicians across numerous specialties. These agents are widely used as contrast for magnetic resonance imaging and have been generally considered safe. Early on, phase III trials and small studies in low-risk patients suggested a benign renal profile; however, more recent studies raised the possibility of nephrotoxicity, although it is not clear whether it approaches the incidence of nephropathy associated with iodinated radiocontrast. In 2006, reports of a rare systemic fibrosing condition called nephrogenic systemic fibrosis (NSF) were recently linked to exposure of patients with advanced kidney disease to GBC agents. Analysis of the data suggests that certain GBC agents are more likely to be associated with NSF. Also, not all patients with kidney disease are at risk for developing NSF, only those with advanced acute or chronic kidney disease. Avoidance of GBC exposure is the best approach for high-risk patients. When GBC is required to obtain optimal images, use of low dosages of more stable macrocyclic agents is safer and preferred. This article reviews the current status of GBC agents as nephrotoxins and causes of NSF and provides opinions on how to use these agents in patients with underlying kidney disease.**

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Magnetic resonance imaging (MRI) scans are significantly enhanced by use of gadolinium-based contrast (GBC) agents. They also have the advantage of avoiding iodinated radiocontrast agents, which have significant overall toxicity. Thus, imaging with GBC agents has been considered a relatively safe alternative to computed tomography scan in situations in which a radiocontrast agent is thought to be required for enhanced image attainment; however, two complications of GBC agents have come to light.

First, concern for GBC-associated nephrotoxicity has been raised as a potential problem in patients with underlying kidney disease. Second and potentially more concerning is the recognition that GBC exposure in patients with advanced kidney disease may trigger the development of nephrogenic systemic fibrosis (NSF) (1–12). This review focuses on the current status of these clinically important complications of GBC agents.

## GBC Agents

### *General Properties*

Gadolinium is a lanthanide metal with paramagnetic properties, which makes it an excellent intravenous and/or intra-arterial contrast agent to improve imaging of various tissues. Because it is a metal, it must be in an ionic form to be soluble in water and allow it to be injected as a contrast agent; however, gadolinium in this free ionic form ($Gd^{3+}$) is highly toxic in humans.

The toxic effects of $Gd^{3+}$ are circumvented by sequestration of the metal by a "chelate" (13). Chelates are large organic molecules that form a stable complex with $Gd^{3+}$ and make the ion biochemically inert and nontoxic (13,14). The GBC agents are classified into four main categories on the basis of their biochemical structure (linear *versus* macrocyclic) and their charge (ionic *versus* nonionic; Figure 1). Macrocyclic chelates bind $Gd^{3+}$ more tightly than linear chelates, tend to be more stable both *in vitro* and *in vivo*, and possess lower dissociation rates (15). The various properties of the chelates have implications for possible toxicity and the risk for liberation of free $Gd^{3+}$ from its chelate, a process known as transmetallation (Figure 2). The characteristics of the commonly used Food and Administration Drug (FDA) approved GBC agents and iodinated radiocontrast agents are noted in Table 1.

### *Pharmacokinetics*

After injection, GBC agents are rapidly distributed into the extracellular space, quickly equilibrating between the plasma and interstitial compartments. They have limited protein binding and do not undergo biotransformation. These agents have small volumes of distribution, approximately 0.3 L/kg body wt. They are eliminated unchanged by the kidneys *via* glomerular filtration. GBC agents maintain a mean terminal half-life ($T_{1/2}$) of approximately 1.3 to 1.6 h. More than 95% of an injected dose is eliminated within 24 h, with <3% being eliminated in the feces (13,14,16). The mean terminal $T_{1/2}$ is prolonged in moderate (5.6 h) and severe (9.2 h; up to 30 h with GFR <5 ml/min) kidney disease as compared with healthy individuals (1.3 to 1.6 h).

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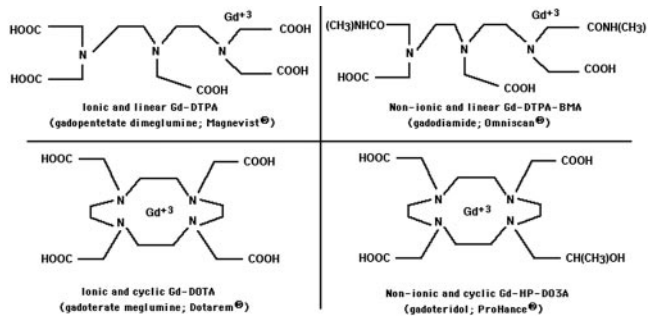


*Figure 1.* Structures of various GBC agents. The agents vary on the basis of linear *versus* macrocyclic structure and ionic *versus* nonionic charge.

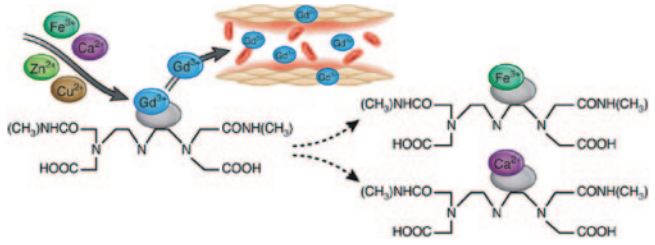

*Figure 2.* The process of transmetallation. A nonionic linear chelate binds $Gd3^+$ less tightly than other chelates, allowing endogenous cations such as copper ($Cu^{2+}$), iron ($Fe^{3+}$), zinc ($Zn^{2+}$), and calcium ($Ca^{2+}$) to compete with $Gd^{3+}$ for chelate binding. This allows free $Gd3^+$ to be released into the circulation, where it may bind other anions such as phosphate.

## GBC Agents and Nephrotoxicity

Iodinated radiocontrast media–induced nephrotoxicity is well described and common in at-risk populations. Radiocontrast-induced nephrotoxicity is associated with significant morbidity, increased hospital length of stay, and increased in-hospital 1- and 5-yr mortality. Because GBC agents have characteristics very similar to those of iodinated radiocontrast (Table 1), in particular hyperosmolality and renal clearance entirely dependent on glomerular filtration, nephrotoxicity was an obvious initial concern. However, GBC agents have significantly lower viscosity and are used at significantly lower volumes (four to 11 times less) than radiocontrast, making them potentially less nephrotoxic. For example, a typical body computed tomography scan uses 150 ml of radiocontrast, whereas a typical MRI study (0.1 to 0.3 mmol/kg) uses 14 to 42 ml of GBC. Thus, the possibility exists that GBC agents could be either similarly nephrotoxic or less nephrotoxic than radiocontrast. As a frame of reference, the nephrotoxicity of GBC agents is compared with that of iodinated radiocontrast agents.

### *Experimental Studies*

GBC agent safety studies using multiple different animals were undertaken using a range of dosages (0.6 to 3.0 mmol/kg). Compared with human dosages, those used in animals ranged from large (0.6 to 1.0 mmol/kg) to massive (1.0 to 3.0 mmol/kg) (17). Minimal increases in blood urea nitrogen and serum creatinine were noted, whereas mild elevations in urinary tubular cell enzymes occurred in exposed animals. When nephrotoxicity developed, it occurred only with high dosages (>1.0 mmol/kg). Histopathology demonstrated vacuolization and necrosis of cortical tubular epithelial cells.

### *Human Studies*

Early studies in healthy individuals as well as patients with mild/moderate levels of underlying kidney disease suggested a favorable renal safety profile (18,19). As a result, the GBC agents were considered relatively safe for use in patients with kidney disease. This led to the frequent use of GBC exposure as a "renal safe" alternative when other imaging techniques were too risky.

### *Absence of Significant Nephrotoxicity with GBC Agents*

As noted in Table 2, several studies suggested that GBC agents lack significant nephrotoxicity (16,18,20–24). Only a few

*Table 1.* FDA-approved GBC agents and iodinated radiocontrast agents[a]

| Agent | Molecular Structure | Charge | Osmolality (mOsm/L) | Viscosity (mPa · S) | Stability Constant | Excess Chelate (mg/ml) |
|---|---|---|---|---|---|---|
| GBC formulation | | | | | | |
| gadodiamide (Omniscan) | Linear | Nonionic | 900 | 1.4 | $10^{14.9}$ | 12.00 |
| gadopentetate (Magnevist) | Linear | Ionic | 1960 | 2.9 | $10^{18.1}$ | 0.40 |
| gadoversetamide (OptiMARK) | Linear | Nonionic | 1110 | 2.0 | $10^{15.0}$ | 28.40 |
| gadobenate (MultiHance) | Linear | Ionic | 1970 | 5.3 | $10^{18.4}$ | 0.10 |
| gadoteridol (Prohance) | Cyclic | Nonionic | 630 | 1.3 | $10^{17.1}$ | 0.23 |
| Iodinated contrast | | | | | | |
| diatrizoate | Monomer | Ionic | 1980 | 6.0 | N/A | N/A |
| iopamidal, iohexol | Monomer | Nonionic | 600 to 1000 | 5.0 to 10.0 | N/A | N/A |
| iodixanol | Dimer | Nonionic | 280 | 11.0 | N/A | N/A |
| iosmenol | Dimer | Nonionic | 280 | 7.0 | N/A | N/A |

[a]FDA, Food and Drug Administration; GBC, gadolinium-based contrast.

*Table 2.* Studies supporting renal safety of GBC agents[a]

| Reference | Study | Contrast Agent | Dosage (mmol/kg) | Renal Function ([Cr] in mg/dl) | Result |
|---|---|---|---|---|---|
| Niendorf *et al.* (18), 1993 | Phase III trial, $n = 1171$ [Cr] at 24 h, subgroup with [Cr] at 5 d | Gadopentetate | 0.10 | [Cr] <1.3, [Cr] >1.3 to 1.4, [Cr] >1.4 | No change in [Cr], Subgroup of patients: GFR 20 to 40: [Cr] ↑ 0.25 GFR <20: [Cr] ↑ 0.25 |
| Arsenault *et al.* (20), 1996 | Retrospective, $n = 136$, $n = 90$ with pre/post [Cr] at 3 d | Gadopentetate | 0.10 | [Cr] >2.0, mean [Cr] 2.5 | No change in [Cr] baseline (2.5) to day 3 (2.3) |
| Prince *et al.* (21), 1996 | Retrospective, $n = 64$, [Cr] 2 d pre and 2 d post, CIN ≥0.5 mg/dl | Gadopentetate, gadodiamide, gadoteridol | 0.20 to 0.40 | [Cr] >1.5, mean [Cr] 2.0 ± 1.4 | CIN: RC- 11/64 (17%) Gado- 0/64 (0%) |
| Swan *et al.* (16), 1999 | Prospective, double-blind random, 32 patients (2:1), CIN >0.5 mg/dl | Gabobenate dimeglumine | 0.20 | CrCl 10 to 30, CrCl 31 to 60, 24-h urine | No CIN |
| Hammer *et al.* (22), 1999 | $n = 31$, 34 DSAs, mean age 53.1, CIN >0.5 mg/dl | Gadopentetate | 0.40 | [Cr] >1.5 | CIN: 1/34 (3%) |
| Spinosa *et al.* (23), 2000 | $n = 40$, LE angiograms, 42 procedures RC- 15, Gado- 20 CIN ≥0.5 mg/dl at 48 h | Gadodiamide | up to 0.40 | [Cr] >1.5, mean [Cr] 2.2, range [Cr] 1.6 to 3.6 | RC- 6/15 (40%) GBC- 1/20 (5%) |
| Spinosa *et al.* (24), 2001 | Consecutive patients treated with Gado + CO2, CIN > 0.5 mg/dl at 48 h | Gadodiamide | <0.30 | [Cr] >1.5, mean [Cr] 2.7 | CIN: 3/95 (3%) |
| Sancak *et al.* (25), 2001 | $n = 16$, intravenous Gado for upper extremity or SVC | Gadodiamide | 0.30 | Mean [Cr] 1.5, range [Cr] 1.2 to 1.8 | Largest increase in [Cr] 0.2 mg/dl |
| Rieger *et al.* (26), 2002 | Prospective, $n = 29$, 32 procedures (IA and intravenous) CIN >0.5 mg/dl at 72 h | Gadopentetate | 0.34 ± 0.06 | [Cr] >1.5 mean [Cr] 3.6 | AKI: 1/29 (atheroemboli) |
| Total | N/A | N/A | Average dosage ~0.26 (0.10 to 0.40) | Average mean [Cr] ~2.36; range 1.2 to 3.6 | CIN: GBC: 0 to 5% RC: 17 to 40% |

[a]CIN, contrast-induced nephropathy; [Cr], serum creatinine concentration; CrCl, creatinine clearance; RC, iodinated radiocontrast; DSA, digital subtraction angiogram; IA, intra-arterial; LE, lower extremity; SVC, superior vena cava.

key studies are discussed in the text. In a phase III trial, 1171 patients were exposed to a 0.1-mmol/kg dose of high osmolar (1960 mOsm/L)/low viscosity (2.9 mPa · S) gadopentetate (18). Patients were grouped according to serum creatinine (<1.3, 1.3 to 1.4, or >1.4 mg/dl) and change in serum creatinine 24 h after GBC agent exposure was examined. No significant change in serum creatinine developed in the three groups. Two small subgroups of high-risk patients with more severe kidney disease (GFR 20 to 40 ml/min [$n = 10$] and GFR <20 ml/min [$n = 5$]) were also evaluated. These groups developed a mean increase in serum creatinine of 0.25 mg/dl at 5 d.

Arsenault *et al.* (20) reviewed 90 of 136 patients who had a mean serum creatinine of 2.5 mg/dl, were exposed to 0.1 mmol/kg gadopentetate, and had pre/post serum creatinine measurements. Day 3 serum creatinine was unchanged (2.5→2.3 mg/dl), suggesting absence of nephrotoxicity. In another study, a cohort of 64 patients with mild chronic kidney disease (CKD; baseline serum creatinine 2.0 ± 1.4 mg/dl) were

examined (21). All patients received both GBC and iodinated radiocontrast at separate times, thereby serving as their own control. The rate of contrast-induced nephrotoxicity, as defined by a rise in serum creatinine of 0.5 mg/dl, was compared between the two different exposures. The dosage of GBC agents administered during the study ranged from 0.2 to 0.4 mmol/kg. No patient who received GBC developed nephrotoxicity as compared with 17% of patients who received iodinated radiocontrast.

Patients with CKD (mean serum creatinine 2.2 mg/dl; range 1.6 to 3.6 mg/dl) were studied to compare nephrotoxicity of nonionic radiocontrast with $CO_2$ supplemented with either GBC (up to 0.4 mmol/kg gadodiamide) or nonionic radiocontrast (23). Forty patients underwent 42 lower extremity angiograms using one of the following contrast protocols: Radiocontrast, gadodiamide, and $CO_2$. Contrast-induced nephropathy (increase in serum creatinine >0.5 mg/dl at 48 h) developed in six (40%) of 15 iodinated radiocontrast studies but only one (5%) of 20 gadodiamide exposures.

Last, 29 patients who had stage 4 CKD (mean serum creatinine 3.6 mg/dl; range 1.6 to 7.0 mg/dl) and received 0.34 mmol/kg gadopentetate were prospectively studied (26). None of the patients developed GBC nephrotoxicity (increase in serum creatinine >0.5 mg/dl) during 3 d of observation. There was no change from baseline mean serum creatinine at 24 and 72 h. One patient developed acute kidney injury (AKI); however, this was attributed to renal atheroemboli.

It is notable that GBC-associated nephrotoxicity developed in 0 to 5% of patients, which was less than iodinated radiocontrast (17 and 40%). The mean baseline serum creatinine in the group was approximately 2.36 mg/dl (range 1.20 to 3.60 mg/dl), and the mean dosage of GBC agent was 0.26 mmol/kg (range 0.10 to 0.40 mmol/kg). Predominantly, intravenous injection of GBC agents was used.

### *Presence of Nephrotoxicity with GBC Agents*

In contrast to the previous reports, a number of studies (27–31) suggested that GBC agents exhibit variable degrees of nephrotoxicity (Table 3). A retrospective study examined the effect of gadopentetate on kidney function in 260 patients, 195 of whom had underlying CKD (27). The average dosage of gadopentetate was 0.28 mmol/kg. Patients who had CKD and received intravenous and intra-arterial gadopentetate had mean baseline serum creatinine of 2.1 and 2.6 mg/dl, respectively. Contrast-induced AKI (increase in serum creatinine >1.0 mg/dl within 48 h) developed in 3.5% of the entire population: 1.9% (three of 153) with intravenous and 9.5% (four of 42) with intra-arterial administration. In the seven patients who developed nephrotoxicity, the average baseline serum creatinine was 2.5 mg/dl; four had diabetes, and five had hypertension. In patients who did not develop AKI, the average baseline serum creatinine was 2.2 mg/dl. Also, the GBC agent dosage was higher in patients with AKI (0.37 mmol/kg) than without AKI (0.27 mmol/kg).

A retrospective study examined 91 patients with stages 3 and 4 CKD for contrast nephrotoxicity (increase in serum creatinine of 0.5 mg/dl within 24 to 72 h) (29). The patients received one of three different GBC preparations (0.2 mmol/kg). Approximately 20% of patients had diabetes and 80% had hypertension. Eleven (12.1%) patients developed AKI, again suggesting that GBC agents can be nephrotoxic. Six of these patients had diabetes, and nine had stage 4 CKD.

Finally, a retrospective study of 163 patients who had CKD and underwent percutaneous renal angiogram for resistant hypertension or ischemic nephropathy compared the rates of contrast-induced AKI among GBC, a mixture of GBC/iodinated radiocontrast, and iodinated radiocontrast alone (31). The majority (81%) of patients had stage 4 CKD. Contrast-induced AKI was defined as an increase in serum creatinine of 0.5 mg/dl within 7 d of the procedure. The groups were well matched with respect to age, diabetes, and hypertension. The baseline estimated creatinine clearance was lower in the GBC agent groups (23.1 ml/min) as compared with the radiocontrast alone group (27.5 ml/min). The GBC group was exposed to a lower dosage of GBC (76 ml) as compared with radiocontrast alone group (102 ml). AKI developed in 5.3% of GBC agent–exposed patients compared with 10.5% in the GBC/radiocontrast group and 20.6% in the radiocontrast alone group ($P < 0.01$).

Table 3 summarizes all of the studies. It is notable that GBC-associated nephrotoxicity developed in 5.3 to 50% of patients, which was equal to or greater than the rate seen with iodinated radiocontrast (6.5 to 45%). The mean baseline serum creatinine in the GBC group was approximately 3.02 mg/dl (range 2.60 to 4.00 mg/dl), and the mean dosage of GBC agent was 0.41 mmol/kg (range 0.20 to 0.60 mmol/kg). In addition, the majority of studies used arterial injection of GBC.

### *GBC Nephrotoxicity: What Is the Bottom Line?*

Data from the studies suffer from use of variable designs with small numbers, patients with varying levels of kidney function, wide ranges of GBC agent dosage, nonuniform measures of kidney function, and poor or no control groups. In general, the majority of studies suggested renal safety, but clearly GBC-induced nephrotoxicity can develop. On balance, it seems that GBC agents are less nephrotoxic than iodinated radiocontrast. This may be due to the lower viscosity of these

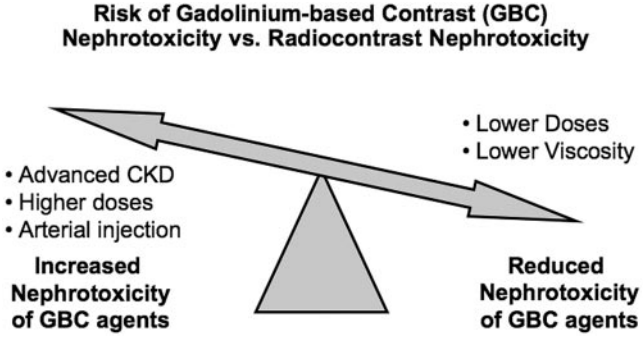


*Figure 3.* On the basis of the published literature, GBC is less nephrotoxic than iodinated radiocontrast; however, when GBC agents are used in high dosage with arterial injection in patients with advanced kidney disease, AKI can occur.

*Table 3.* Studies supporting nephrotoxicity of GBC agents[a]

| Reference | Study | Contrast Agent | Dosage (mmol/kg) | Renal Function ([Cr] in mg/dl) | Result |
|---|---|---|---|---|---|
| Sam *et al.* (27), 2003 | $n$ = 195 with CKD, no control group CIN >1.0 mg/d at 48 h with oligoanuria | Gadopentetate | 0.28 | CrCl <80 ml/min, CG 38.2 ± 16 ml/min, mean [Cr] 2.6 | CIN: 7/195, MRA: 3/153 (1.9%), DSA: 4/42 (9.5%) |
| Erley *et al.* (28), 2004 | Randomized prospective, $n$ = 21, CIN >50%, decrease in GFR | Gadobutrol = 10 Iohexol = 11 | 0.57 ± 0.17 | [Cr] >1.5 or CrCl <50 ml/min per 1.73 $m^2$, mean [Cr] 3.4 | CIN: GBC: 5/10 (50%) RC: 5/11 (45%) |
| Briguori *et al.* (30), 2006 | Retrospective, $n$ = 25 (historical controls, $n$ = 32), CIN ≥0.5 mg/dl within 48 h or dialysis within 5 d | Gadodiamide = 8 Gadobutrol = 17 3:1 mixture with RC | 0.60 ± 0.30 0.28 to 1.23 | [Cr] >2 mg/dl or CrCl <40 ml/min, mean [Cr] 2.3 | CIN: GBC: 7/25 (28%); RC: 2/32 (6.5%) |
| Ergun *et al.* (29), 2006 | Retrospective, $n$ = 91, [Cr] measured pre-GBC, days 1, 3, and 7, and 1 mo, CIN ≥0.5 mg/dl within 72 h | Gadopentetate, gadodiamide, dotarem | 0.20 | Stages 3 and 4 CKD mean [Cr] 33 ml/min, range CrCl 15 to 58, mean [Cr] 4.0 | CIN: 11/91 (12.1%); CKD Stage 4: 9/11 with CIN |
| Kane *et al.* (31), 2008 | Retrospective, $n$ = 163, [Cr] measured pre-GBC and within 7 d, CIN ≥0.5 mg/dl within 7 d | GBC agent, GBC + RC mixture, RC alone | GBC-76 ml, GBC + RC mixture-55 + 37 ml, RC-102 ml | Stages 3 to 5 CKD GBC [Cr] 2.77, GBC + RC [Cr] 2.63, RC [Cr] 2.48 | CIN: GBC: 5.3% GBC + RC: 10.5%; RC: 20.6% |
| Total | N/A | N/A | Average dosage ~0.41 (0.20 to 0.60) | Average mean [Cr] ~3.02, range 2.60 to 4.00 | CIN: GBC: 5.3 to 50.0%; RC: 6.5 to 45.0% |

[a]MRA, magnetic resonance angiography.

agents as well as the much lower volume of contrast required for imaging. That being said, there seem to be adequate data to suggest that GBC agents have enough of a nephrotoxic potential that caution should be exercised with their use in patients with stages 4 and 5 CKD. Higher dosages of GBC agents and intra-arterial injection also are likely risk factors for development of AKI in at-risk patients (Figure 3).

## GBC and Nephrogenic Systemic Fibrosis

*Nephrogenic Systemic Fibrosis: A New Disease*

A previously unrecognized fibrosing disorder of the skin that was histologically similar to scleromyxedema was noted in nine renal transplant recipients who required long-term dialysis, five patients with ESRD, and one patient with AKI (7). After a publication describing the cases, the disease was initially called a "scleromyxedema-like disorder of renal dialysis patients." In a subsequent publication, the entity was descriptively coined "nephrogenic fibrosing dermopathy" (7). The subsequent recognition that fibrosis also occurred in systemic organs led to a new name for the disease: "Nephrogenic systemic fibrosis" (NSF).

*GBC Agents: The NSF Trigger?*

After the initial report of cases, the NSF literature consisted predominantly of case reports/case series with the cause being ascribed to any of a number of potential agents or associations. In 2006, a major breakthrough occurred when Grobner (2) reported the development of NSF in five patients who had ESRD and were exposed to gadodiamide. Subsequently, Marckmann *et al.* (3) described 13 patients (ESRD and stage 5

CKD) who developed symptoms of NSF within 2 to 75 d after gadodiamide exposure. A number of publications have verified this association (4,5,32–35). Table 4 demonstrates the odds ratio for developing NSF in exposed *versus* unexposed patients with ESRD/CKD from five case-control studies (4,32,35–37).

### *Evidence to Incriminate GBC Agents in NSF*

Further evidence of the importance of GBC agents as a trigger for NSF was provided by documentation of $Gd^{3+}$ within the tissues of patients with NSF using scanning electron microscopy and energy dispersive x-ray spectroscopy (38,39). High *et al.* (40) also quantified the concentration of $Gd^{3+}$ in tissues of the patients who had NSF and were previously examined. They found that the NSF tissues contained 35- to 150-fold higher amounts than the tissues of healthy individuals who were exposed to GBC. Others have confirmed these findings with even more sensitive techniques (41).

### *Are Certain GBC Agents More Likely to Cause NSF?*

A complete review of the published literature on the association of GBC agents with NSF put the risk for NSF with certain GBC agents into perspective (42). A total of 190 cases of biopsy-proven NSF were identified using PubMed/MEDLINE. Gadodiamide was the culprit GBC agent in 157 cases; gadopentetate ($n = 8$) and gadoversetamide ($n = 3$) were the others noted. In the remaining cases, 18 were unspecified, four were confounded, and five were purported to have no GBC agent exposure.

A recently published retrospective study examined the relationship of GBC exposure and biopsy-proven NSF at four US academic medical centers (43). They collected data on type and cumulative dosage of GBC administered and calculated a benchmark incidence at the medical centers. Two centers used only gadodiamide; the other two centers used only gadopentetate. They found that predominantly patients with stage 5 CKD developed NSF after large cumulative GBC dosages. The benchmark incidence of NSF was one in 44,224 with gadopentetate and one in 2913 with gadodiamide. This calculates to an odds ratio of 13 for developing NSF with gadodiamide compared with gadopentetate.

In a recent publication that examined the FDA MedWatch reporting system data as of October 2007, numerous cases of NSF associated with exposure to GBC agents were reported (44). Gadodiamide was noted in 283 cases (246 alone) and gadopentetate in 125 (96 alone), the most common. It is interesting that gadoteridol, which has the third greatest market share, had the least number of reported NSF cases, with only one case noted with exposure to gadoteridol alone.

An important retrospective study that shed light on the different risk potential of the various GBC agents was recently published (44). In that study, 141 patients with ESRD had 198 gadoteridol (macrocyclic nonionic chelate) exposures during a 7-yr period (2000 through 2007). The majority of exposures were single ($n = 104$), but several were two or greater ($n = 37$). No cases of NSF were noted during this period, clearly less than the 2 to 18% prevalence described with gadodiamide exposure.

Recently, 42 rats with normal kidney function were exposed to various types of high-dosage GBC agents (gadodiamide, gadoversetamide, gadopentetate, gadobenate, gadobutrol, and gadoterate) or saline control daily for 28 d (45). Rats exposed to gadodiamide developed NSF-like skin lesions at 5 d, whereas the rest of the rats did not. Histopathology identical to NSF was noted only in the gadodiamide-exposed rats. Gadolinium tissue concentrations were highest in gadodiamide-exposed rats followed by gadoversetamide and gadopentetate. Although gadolinium was present in the other three groups, the gadolinium concentrations were approximately 30-fold lower in these rats.

### *Why Is Gadodiamide More Frequently Associated with NSF?*

One theory to explain the gadodiamide association relates to its stability, defined as the ability of the chelate to bind to and sequester $Gd^{3+}$. Gadodiamide has the lowest stability constant and highest dissociation rate of the five GBC preparations available in the United States (Table 1). Because of this decreased stability, the $Gd^{3+}$ ion of gadodiamide is more likely to dissociate from its chelate than other GBC agents. Reduced kidney function significantly increases the $T_{1/2}$ of GBC agents as they are slowly excreted by the kidneys. Thus, significant renal impairment is associated with increased time for transmetallation (Figure 2) and prolonged tissue exposure, which may promote deposition of toxic $Gd^{3+}$, leading to fibrosis. This process is less likely to occur with the more stable macrocyclic chelates.

### *Which Patients Are at Highest Risk to Develop NSF after GBC Exposure?*

The published literature clearly documents that patients with advanced kidney disease are at highest risk to develop NSF after GBC agent exposure. Nearly 80% of patients have ESRD and are on dialysis, whereas the rest have primarily stage 5 CKD and AKI. A small number of patients have been described

*Table 4.* Case-control studies with odds ratio for patients who had ESRD/CKD and were exposed to GBC agents

| Reference | No. of NSF Cases | No. of Patients with ESRD and Exposure to GBC | Odds Ratio |
|---|---|---|---|
| Broome *et al.* (4) | 12 (ESRD 8) | 258 | 41.3 |
| Collidge *et al.* (36) | 14 (12 biopsy-proven) | 1418 | 46.6 |
| Deo *et al.* (32) | 3 | 380 | 31.5 |
| Othersen *et al.* (37) | 4 | 588 | 20.6 |
| Marckmann *et al.* (35) | 13 (ESRD 8) | 430 | 32.5 |

with stage 4 CKD (approximately five). It is important to note that no cases of stages 1 through 3 have been reported in the published literature. In fact, several studies that included patients who had stages 1 through 4 CKD and were exposed to GBC agents had not noted NSF as a complication. In the HALT-Polycystic Kidney Disease and Consortium for Radiologic Imaging Studies of PKD (CRISP), patients with autosomal dominant polycystic kidney disease and stages 1 through 3 CKD underwent 1111 GBC agent exposures with no cases of NSF developing (46). Patients who had stages 3 and 4 CKD ($n = 592$) and were exposed to GBC also did not develop NSF (37). Finally, patients who had stages 1 through 4 CKD ($n = 88$) and underwent 94 GBC agent exposures, including 38 patients with stage 4 CKD, did not develop NSF (47). On the basis of the literature, stage 4 CKD seems to be very low risk.

*GBC and NSF: The Bottom Line*

On the basis of the current published literature, a couple of conclusions can be drawn. First, patients who are at highest risk to develop NSF after GBC agent exposure are those with ESRD, stage 5 CKD, and AKI. Patients with stage 4 CKD maintain some risk, but it is likely much lower than the aforementioned groups. There seems to be little or no risk for patients with stages 1 through 3 CKD. Clearly, patients with normal kidney function have no risk.

The risk associated with the various GBC agents is likely different as well. Gadodiamide, the linear nonionic chelate–based formulation, maintains the highest risk on the basis of epidemiologic data and animal studies. Gadopentetate, the linear ionic chelate–based product probably has a medium risk, less than the linear nonionic chelates but more than the macrocyclic chelates. Gadoteridol, the only FDA-approved macrocyclic chelate, maintains less risk. Clearly, high dosages and large cumulative dosages of these agents will increase risk for NSF.

## Current Status of GBC Agents in Kidney Disease

Because there is no effective therapy for NSF, avoidance of exposure by using alternative imaging modalities is the best option. This would entail identifying the high-risk groups. If an imaging test using a GBC agent is required, then a discussion with the health care providers and patient should ensue to discuss the risks and benefits. Once informed consent is obtained and documented, I recommend the following approach:

1. Use a macrocyclic chelate (gadoteridol in the United States), avoiding linear chelates.
2. Use the lowest dosage of GBC agent possible to achieve the image.
3. Avoid repeat exposures with GBC agents.
4. Consider performing hemodialysis after the exposure (and the next 2 d) in patients who are already maintained on hemodialysis, recognizing that there are no data that support prevention of NSF with this modality. The recommendation is based on the pharmacokinetics of GBC and the theoretical benefit of removing it with hemodialysis (>95% plasma clearance). In contrast, peritoneal dialysis clears GBC poorly.

## Conclusions

GBC agents can no longer be assumed to be as safe as they have traditionally been considered in patients with underlying kidney disease. Although less nephrotoxic than iodinated radiocontrast, GBC agents can cause AKI in high-risk patients who receive large dosages and/or intra-arterial injections. NSF can be a catastrophic complication of GBC agent exposure; avoidance in high-risk patients, when possible, is the best measure to prevent the disease. If GBC agent exposure is required, then using the smallest dosage of a macrocyclic chelate is the next best option. Hemodialysis should be considered after GBC agent exposure in patients who are already on this modality.

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## Disclosures

None.

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## Correction

Erratum for Perazella: Current Status of Gadolinium Toxicity in Patients with Kidney Disease. Clin J Am Soc Nephrol 4: 461–469, 2009

There was an error in Table 4, and the acknowledgement was not included.

Table 4 was created and provided by Dr. Ali-Abu-Alfa (Section of Nephrology, Yale University). The author would like to thank him for his kindness in sharing the table. To permit the calculation of the odds ratios for cohorts with no NSF cases in unexposed ESRD patients, 0.5 was added to each cell in the contingency table (Haldane's estimator).

*Table 4*. Case-control studies with odds ratio for patients who had ESRD and were exposed to GBC agents

| Author (ref) | No. of NSF Cases | No. of Exposed/Unexposed ESRD patients | Odds Ratio |
|---|---|---|---|
| Collidge *et al.* (36) | 14 | 421/1405 | 44.7 |
| Deo *et al.* (32) | 3 | 87/380 | 31.5 |
| Othersen *et al.* (37) | 4 | 261/588 | 20.6 |
| Markmann *et al.* (35) | 13 (8 ESRD) | 370/430 | 20.2 |


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