

# NEPHROGENIC SYSTEMIC FIBROSIS

## (Revision performed with input from and approval of the ACR Subcommittee on MR Safety)

### Definition

Nephrogenic systemic fibrosis (NSF) is a fibrosing disease, primarily identified in the skin and subcutaneous tissues but also known to involve other organs, such as the lungs, esophagus, heart, and skeletal muscles. Initial symptoms typically include skin thickening and/or pruritis. Symptoms and signs may develop and progress rapidly, with some affected patients developing contractures and joint immobility. Death may result in some patients, presumably as a result of visceral organ involvement.

### Associations

#### *Gadolinium-based contrast medium (GBCM) administration*

When first described in 2000, NSF was noted to occur predominantly in patients with end stage chronic kidney disease (CKD), particularly in patients on dialysis. Initially, no other consistent association was identified; however, in 2006 several groups noted a strong association with gadolinium-based contrast media (GBCM) administration to patients with advanced renal disease and the development of NSF [1,2].

Much about NSF is still controversial and/or unknown at least to some extent, including the following: precise quantification of the relative risk of NSF development following administration of the various GBCM; causation; the relative roles of the free gadolinium ion and/or the ligand component of GBCM; requirement for additional risk factors and what they may be (why don't all

at-risk patients develop NSF?); and whether post-GBCM hemodialysis can reduce the risk of subsequent development of NSF.

Regardless of these unresolved issues, empirical data and theoretical lines of reasoning suggest that not all GBCM are associated with an identical risk of NSF in at-risk patients. The majority of studies have reported on the incidence of NSF after gadodiamide exposure. When considering market share data, either gadopentetate dimeglumine or gadoversetamide would be the next most frequently implicated agent. In response, the European Medicines Agency (EMA) classified GBCM into different groups (when considering administration to at-risk patients) [3], as data has suggested that some agents may be less likely to be associated with NSF in high-risk (severe renal failure) patients than others. In a modification of the EMA system, at the present time, the ACR Committee on Drugs and Contrast Media and the ACR Subcommittee on MR Safety prefer to categorize GBCM into the following three groups listed beginning on the following page.

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

Gadodiamide (Omniscan<sup>®</sup> – GE Healthcare)  
Gadopentetate dimeglumine (Magnevist<sup>®</sup> – Bayer HealthCare Pharmaceuticals)  
Gadoversetamide (OptiMARK<sup>®</sup> – Covidien)

As of December, 2009, according to data provided by the Food and Drug Administration (FDA) [4], the approximate number of administered doses and the number of NSF cases associated with these three agents were as follows:

<b>Agent</b>	<b>Approximate # of doses (in millions)</b>	<b># of reported NSF cases <i>Single Agent (nonconfounded)</i></b>
<b>Gadodiamide</b>	13	382
<b>Gadopentetate dimeglumine</b>	23	195
<b>Gadoversetamide</b>	4.7	35

While various factors may have influenced the number of cases reported with each of these agents, investigators believe that intrinsic properties of these three agents increase the relative likelihood of NSF developing following exposure in at-risk patients.

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

Gadobenate dimeglumine (MultiHance<sup>®</sup> – Bracco Diagnostics)  
Gadoteridol (ProHance<sup>®</sup> – Bracco Diagnostics)  
Gadoteric acid (Dotarem<sup>®</sup> – Guerbet) - as of this writing not FDA-approved for use in the United States.  
Gadobutrol (Gadovist<sup>®</sup> – Bayer HealthCare Pharmaceuticals) – as of this writing not FDA-approved for use in the United States.

**Group III: Agents which have only recently appeared on the market in the US:**

Gadofosveset (Ablavar<sup>®</sup> – Lantheus Medical Imaging)  
Gadoxetic acid (Eovist<sup>®</sup> – Bayer HealthCare Pharmaceuticals)

There is limited data for these agents, although, to date, few, if any, unconfounded cases of NSF have been reported.

The differences in frequency among the various GBCM with which NSF has been associated may reflect a combination of factors, including agent toxicity [1,2,4-8], and market share.

NSF is believed to occur more commonly in patients who have received high doses of GBCM as well as in patients who have received higher cumulative lifetime doses of

these agents. Thus, reported frequency may also have been affected if some agents were used at higher doses disproportionately more frequently than others. However, almost half of the patients with biopsy-proven NSF in the International Center for NSF research (ICNSFR) data registry contracted the disease following a single administration, one-third having had magnetic resonance angiography (MRA) [Cowper S,

Presentation at December 8, 2009 Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees re: Safety Considerations Related to FDA-Approved Gadolinium-Based Contrast Agents Used with Magnetic Resonance Imaging (MRI) Scans. Hilton Washington DC North/Gaithersburg, Gaithersburg, MD].

If release of free gadolinium ion ultimately proves to be the mechanism for the causation of NSF (see below), it is reasonable to postulate that differences in frequency may, in part, be explained by differences in the chemical properties of the different GBCM. At the same time, no GBCM may be completely free of NSF risk (since all GBCM can release some amount of free gadolinium).

A number of studies have noted that the time between injection of GBCM and the onset of symptoms within days to six months in the vast majority of patients [1,2,8-11]; however, in rare cases, symptoms have appeared years after the last reported exposure [11]

#### *Chronic kidney disease*

Based upon current knowledge it is estimated that patients with severe CKD (CKD4 and CKD5, which corresponds to eGFR values of 15-29 and <15 ml/min/1.73m<sup>2</sup>, respectively) have a 1% to 7% chance of developing NSF after exposure to GBCM [1,2,5,8-11]; however, in some series including selected subgroups of patients, the reported incidence has been as high as 18% [12]. There have been a few isolated reports of biopsy-proven NSF developing in patients with CKD3 (which corresponds to an estimated glomerular filtration rate (eGFR) value between 30 and 59 ml/min/1.73m<sup>2</sup>); however, in most of these cases, the measured eGFR was closer to the lower end of this range [13].

#### *Acute kidney injury*

NSF has also developed in patients with acute kidney injury [14], even if renal function subsequently returned to normal following GBCM administration [15]. In one series, up to 20% of NSF cases were diagnosed in patients who had been in some element of transient acute renal failure (often, but not always, superimposed upon chronic kidney disease) at the time of GBCM administration [16].

#### *High-dose and multiple exposures*

Many of the published series have suggested that renal failure patients are at highest risk when they are exposed to high doses or multiple doses of GBCM. Nonetheless, there are clearly reported instances of NSF occurring in patients who have been exposed to standard (0.1 mmol/kg) single doses of GBCM [11,17] or exceptionally rarely in those who have no known GBCM exposure [18]. Considering that patients may have received GBCM at other institutions without realizing that this was the case, it is certainly quite possible that some of the patients with no known GBCM exposure received GBCM in the past. Conversely, there are also patients with severe CKD, who have received high doses and/or many doses of GBCM, but who have not developed NSF [11]. In one study [19], of 30 patients who had an eGFR of under 30 ml/min/1.73m<sup>2</sup> and who were exposed to high doses of gadodiamide (median dose of 90 ml and range of 40 to 200 ml), only one patient subsequently developed NSF, which calculates to an incidence of only about 3%.

#### *Total cumulative dose of GBCM*

Several articles have suggested that there is a direct relationship between total cumulative dose (over months or years), and the severity [2] and likelihood of NSF [8,20].

### *Other possible risk factors*

A number of other factors have been postulated to explain why some patients with severe CKD who are exposed to GBCM develop NSF and some do not. These include metabolic acidosis or medications that predispose patients to acidosis [1,6], increased iron, calcium, and/or phosphate levels [6,21], high-dose erythropoietin therapy, immunosuppression [8], vasculopathy [22], an acute pro-inflammatory event [10,23], and infection [24], all at the time of GBCM exposure. None of these potential risk factors has been demonstrated consistently to be present in all affected patients in all studies. Therefore, at the present time, none of these risk factors can be considered to have been established as a true co-factor with a high degree of confidence.

### *Hepatic insufficiency / hepatorenal syndrome*

Initially, a number of researchers observed that a disproportionate number of affected patients had severe liver as well as renal dysfunction [10,11], prompting the FDA to warn against the use of GBCM in patients with "...acute renal insufficiency of *any severity* due to the hepatorenal syndrome or in the perioperative transplantation period" [25]. Most of the more recent series have not supported this conclusion. For example, in one study, a review of the literature found that of 291 NSF patients, 34 (12%) had concomitant liver disease [26]; however, all but one of these patients also had known severe renal insufficiency (eGFR of <30 ml/min/1.73m<sup>2</sup>) prior to GBCM administration.

### **Postulated Mechanism**

The exact mechanism of NSF causation is unknown; however, the most widely held theory is that the gadolinium ion dissociates from its chelate in patients with significantly degraded renal function due to the prolonged clearance times of the GBCM in these

patients, as well as to other metabolic factors associated with this level of renal disease. This dissociation occurs by a process known as transmetallation, whereby other cations replace the gadolinium associated with the chelate. Suspected cations include protons (in acidic environments), calcium, iron, zinc, copper, fosrenol, and rare metals. The free gadolinium then binds with other anions (such as phosphate or bicarbonate), and the resulting insoluble precipitate is deposited in the skin and subcutaneous tissues (as well as at other locations) via a process that is still poorly understood [5,27]. A fibrotic reaction ensues, involving the activation of circulating fibrocytes [27,28]. This is supported by the greater presence of gadolinium in affected tissues of NSF patients relative to unaffected tissues [29]. It has not yet been determined whether this deposited gadolinium is free or chemically bound in the initial gadolinium-chelate form or perhaps in the form of a newly-formed other gadolinium-bound moiety. It is noteworthy, however, that the detection of gadolinium in tissue samples may not be required for diagnosis.

Given differences in *in vitro* stability, it is likely that all GBCM are not equally prone to transmetallation *in vivo*. If gadolinium dissociation from its chelate is eventually proved to contribute to, or be primarily responsible for, the development of NSF in many patients, this may help explain why the various GBCM differ in their apparent NSF safety profiles in at-risk patients [30].

### **Recommendations for Identifying High-Risk Groups**

It is important to identify patients who are at increased risk of developing NSF prior to any GBCM injection. Patients at highest risk are those who have severe chronic kidney disease (generally defined as patients who have eGFRs of <30 ml/min/1.73m<sup>2</sup>) [31,32] or acute kidney injury [31,32].

Patients can be screened verbally to identify the presence of a history of renal disease;

however, such screening has been shown to fail to detect many patients with moderate, severe, and end stage chronic kidney disease [33]. Many experts (including the American College of Radiology Subcommittee on MR Safety) have recommended that an eGFR be obtained within six weeks of anticipated GBCM injection in patients who might have reduced renal function. It has been suggested that this would include any patients with a history of renal disease (including a solitary kidney, renal transplant, or renal neoplasm), anyone over the age of 60 years, and patients with history of hypertension or diabetes mellitus [34].

It is recommended for adults that eGFR calculation should be performed using the Modification of Diet in Renal Disease (MDRD) equation. The four-variable MDRD equation takes into account patient age, race, gender, and serum creatinine level. The Schwartz equation should be used for children (also see Chapter on Contrast Media in Children). While a number of Internet sites are now available which can calculate eGFR values in adults and children, the isotope dilution mass spectrometry (IDMS)-traceable MDRD and updated Schwartz equations are also provided here.

*MDRD equation:*

$eGFR (mL/min/1.73 m^2) = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

*Updated Schwartz equation:*

$eGFR (mL/min/1.73 m^2) = (0.413 \times \text{height in cm}) / \text{serum creatinine in mg/dl}$

Obviously, decisions concerning the appropriate time interval between the last eGFR determination and GBCM injection will be tempered by any interval change in the patient's clinical condition (which might increase the need for a more recent eGFR).

## **Recommendations for Imaging High-Risk Patients**

Once a high risk patient is identified, a number of additional recommendations can be made [31,32], including considering alternative studies that do not require GBCM injection, informing such patients about the potential risks of GBCM-enhanced magnetic resonance imaging (MRI) studies should such studies be deemed necessary despite the risks, using the lowest possible dose of GBCM required to obtain the needed clinical information, avoiding double or triple dose studies, and avoiding the use of those GBCM that have been most frequently associated with NSF (which, as of June 1, 2010 include gadodiamide [Omniscan<sup>®</sup>], gadopentetate dimeglumine [Magnevist<sup>®</sup>], and gadoversetamide [OptiMARK<sup>®</sup>]). It is also recommended that the referring physician and patient be informed of the risks of GBCM administration and that both the patient and his or her referring physician agree with the decision to proceed after demonstrating an understanding of the potential risks of the procedure and possible alternate imaging/diagnostic options.

Precautions such as these have already had a dramatic effect in reducing or even eliminating the number of NSF cases that are being encountered [35]. It must be remembered that the risks of administering GBCM to a given high-risk patient must always be balanced against the often substantial risks of not performing a needed contrast enhanced imaging procedure.

### **Specific Recommendations**

*Patients with end-stage renal disease on chronic dialysis*

If a contrast-enhanced cross-sectional imaging study is required in an anuric patient with no residual renal function, it would be reasonable to consider administering iodinated contrast media and

performing a CT rather than an MR, if such a substitution is deemed feasible.

If a contrast-enhanced MR examination must be performed in a patient with end-stage renal disease on chronic dialysis, avoidance of group I agents (see above) is recommended. Also, use of the lowest possible dose needed to obtain a diagnostic study is suggested, and is recommended as appropriate for all patients regardless of renal status. The ACR Committee on Drugs and Contrast Media and the ACR Subcommittee on MR Safety also recommend that GBCM-enhanced MRI examinations be performed as closely before hemodialysis as is possible, as prompt post-procedural hemodialysis may reduce the likelihood that NSF will develop. However this has not been proved definitively to date. NSF has developed in patients who have received hemodialysis occurring as soon as 9 hours following GBCM administration [36]. Because it may be difficult for a busy dialysis center to alter dialysis schedules at the request of imaging departments, it may be more feasible for elective imaging studies to be timed to precede a scheduled dialysis session.

While it is possible that multiple dialysis sessions may be more protective than merely a single session, this possible incremental benefit remains speculative, and is based entirely on the theory that prolonged retention of gadolinium-chelate may in some way be associated with the ultimate development of NSF. Still, many experts recommend that consideration be given to the performance of several dialysis sessions following GBCM administration, with use of prolonged dialysis times and increased flow rates and volumes to assist in the process of GBCM clearance. Peritoneal dialysis provides much less potential NSF risk reduction compared to hemodialysis and should not be considered protective.

*Patients with CKD 4 or 5 (eGFR <30 ml/min/1.73m<sup>2</sup>) not on chronic dialysis*

The correct course of action in this patient group is problematic, as administration of iodinated contrast media for CT could worsen renal function and lead to the need for dialysis, while administration of GBCM for MRI could lead to NSF.

It is recommended that any contrast media administration be avoided in this group of patients, if feasible. If MRI contrast media administration is deemed essential, judicious use of the lowest possible dose needed to obtain a diagnostic study is recommended. Although there is no absolute proof that any GBCM is completely safe in this patient group, it is recommended that Group 1 agents (see above) be avoided if GBCM is deemed necessary. Further, it may be prudent to avoid re-administration of GBCM for several days to a week (with the precise duration of delay balanced with the severity of renal disease and medical urgency in a particular patient).

*Patients with CKD 3 (eGFR 30 to 59 ml/min/1.73m<sup>2</sup>)*

Some investigators have recently suggested that these patients be divided into two subgroups:

CKD 3a (eGFR of 45 - 59 ml/min/1.73m<sup>2</sup>),  
and  
CKD 3b (eGFR of 30 - 44 ml/min/1.73m<sup>2</sup>).

(From: Proposed Modifications to the CKD classification system from the Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on Chronic Kidney Disease: Definition, Classification, and Prognosis; London, October, 2009.)

The risk of NSF development in CKD 3a patients is exceedingly small and at this time the only precaution recommended in these patients would be to ensure that the lowest dose of GBCM be administered to obtain a

diagnostic study. In particular, a decision to administer a Group I agent to these patients should be made only following appropriate risk-benefit assessment.

The risk of NSF development in CKD 3b patients is also exceedingly small (as long as a dose of GBCM of 0.1 mmol/kg or less is utilized), albeit not zero. Since eGFR determinations may fluctuate from one day to the next, CKD 3b patients with eGFR levels approaching 30 ml/min/1.73m<sup>2</sup> may actually have similar risks to CKD 4 patients (as they might be classified as having CKD 4 at other times). Thus, similar precautions as those mentioned for CKD 4 and CKD 5 patients, directly above, could be considered in this subset of CKD 3b patients.

#### *Patients with CKD 1 or 2 (eGFR 60 to 119 ml/min/1.73m<sup>2</sup>)*

There is no evidence that patients in these groups are at increased risk of developing NSF. Current consensus is that all GBCM can be administered safely to these patients.

#### *Patients with acute kidney injury (AKI)*

Patients with AKI who have been exposed to GBCM are at risk for developing NSF [15]. Due to the temporal lag between serum creatinine values and actual glomerular filtration rates, it is not possible to determine whether a given patient is in AKI based on a single eGFR determination. Accordingly, caution should be exercised in use of GBCM in patients with known or suspected AKI regardless of measured serum creatinine or calculated eGFR values. GBCM should only be administered to these patients if absolutely necessary. When GBCM administration is required, avoidance of agents associated with the greatest apparent NSF-associated risk (Group I agents) is preferred. Use of the lowest possible dose needed to obtain a diagnostic study is also strongly suggested.

#### *Patients with ascites*

In patients with ascites, GBCM may accumulate within the peritoneal cavity after intravenous administration. Prolonged residence of GBCM in the peritoneal cavity would theoretically increase the risk of NSF. However, there have been no reports of NSF developing in individuals with ascites who do not have underlying severe renal insufficiency. The number of exposures in this population is unknown. The risk of NSF in patients with ascites and normal renal function is not yet defined but is likely to be small. Thus, further investigation is needed to define the risk (if any) of ascites in the absence of renal insufficiency.

#### *Pregnant patients*

GBCM can accumulate in amniotic fluid, which could theoretically increase the risk of maternal and/or fetal NSF. For this reason, GBCM should not be administered in this group unless no alternative imaging study is available and a contrast-enhanced MR scan is absolutely necessary. However, there have been no reports of NSF developing in pregnant women or fetuses/neonates, although the number of exposures in these patients is unknown and likely small.

#### *Children*

At this time (mid 2010), very few pediatric cases of NSF have been reported, and no cases have been reported in children under the age of 6 years. Nevertheless, there is not enough data to suggest that NSF is less likely to occur in children than in adults with similarly significant renal disease. Therefore, it is prudent to follow the same guidelines for adult and pediatric patients as described in the remainder of this document. It should be noted that eGFR values in certain premies and neonates may be <30 ml/min/1.73m<sup>2</sup> simply due to “immature” renal function (and not due to pathologic renal impairment). In these individuals, we believe that caution should still be used when administering GBCMs, although an

eGFR value <30 ml/min/1.73m<sup>2</sup> should not be considered an absolute contraindication to GBCM administration.

### Caveat

Information on NSF and its relationship to GBCM administration is still evolving, and the summary included here represents only the most recent opinions of the ACR Committee on Drugs and Contrast Media and the ACR Subcommittee on MR Safety (as of June 3, 2010). As additional information becomes available, our understanding of causative events leading to NSF and recommendations for preventing it may change, leading to further revisions of this document.

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