

Nephrogenic Systemic Fibrosis (NSF)

Definition

Nephrogenic systemic fibrosis (NSF) is a fibrosing disease, primarily involving 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. In some patients, the disease may be fatal.

Associations

Gadolinium-based contrast agent (GBCA) 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. In 2006 several groups noted a strong association between gadolinium-based contrast agent (GBCA) administration in patients with advanced renal disease and the development of NSF [1,2], and it is now generally accepted that GBCA exposure is a necessary factor in the development of NSF. The time between injection of GBCA and the onset of NSF symptoms occurs within days to months in the vast majority of patients [1-6]; however, in rare cases, symptoms have appeared years after the last reported exposure [5].

While the association between NSF development and exposure to GBCAs is well accepted, the precise relationship between NSF and different formulations of GBCAs is controversial and incompletely understood. Some GBCAs have been associated with few, if any, confirmed cases of NSF, and most unconfounded cases have been reported after exposure to gadodiamide, gadopentetate dimeglumine, and/or gadoversetamide. If the prevailing hypothesis is true – that the development of NSF is related to the release of gadolinium from the chelates that constitute GBCAs – the differences in number of reported cases may, in part, be explained by differences in chemical properties of different GBCAs. However, a combination of other factors, including market share, number of years that the agent has been in use, and possible reporting bias, also may contribute to differences in number of reported cases associated with the various GBCAs.

Utilizing both empirical data and theoretical lines of reasoning, the ACR Committee on Drugs and Contrast Media, the European Medicines Agency (EMA), and the U.S. Food and Drug Administration (FDA) all have classified GBCAs into different groups (see Table at end of chapter) based on reported associations with NSF in vulnerable patients, although the scheme used by each is not identical [7,8].

Chronic kidney disease

Based upon current knowledge, it is estimated that patients with end-stage CKD (CKD5, eGFR <15 ml/min/1.73 m²) and severe CKD (CKD4, eGFR 15 to 29 ml/min/1.73 m²) have a 1% to 7% chance of developing NSF after one or more exposures to at least some GBCAs [1-6,9].

However, most patients who developed NSF had end-stage kidney disease and were on dialysis at the time of exposure. Moreover, among patients with severe CKD (CKD4) that developed NSF (approximately 3% of all reported NSF cases), most had an eGFR closer to 15 ml/min/1.73 m² than to 30 ml/min/1.73 m². There has been only one published case report of a patient with eGFR values above 30 ml/min/1.73 m² [10].

Acute kidney injury (AKI)

Between 12% and 20% of confirmed cases of NSF have occurred in patients with AKI, often superimposed upon CKD [11,12]. Some cases of NSF have developed in patients with AKI without underlying CKD [13]. Hence, AKI alone is also a risk factor for NSF development in the consensus opinion of the ACR Committee on Drugs and Contrast Media.

High-dose and multiple exposures

Cases of NSF have occurred following a single exposure to a GBCA, including a single exposure to a standard (0.1 mmol/kg) single dose [5,14]. A few cases of NSF also have been reported in patients with no known GBCA exposure [15]. In some of these cases, subsequent tissue biopsy evaluation revealed elevated gadolinium levels in the tissues of these patients, suggesting that at least some of these patients had prior unknown GBCA exposure [16].

Nevertheless, NSF is believed to occur most commonly in patients who have received high doses of GBCA, either as a single administration or cumulatively in multiple administrations over months to years [6,17]. Thus, the reported frequency of associations with the various types of GBCAs may be skewed if specific agents were preferentially used at higher doses or more often than others, especially in vulnerable patients.

Importantly, most patients with severe CKD exposed to high doses and/or many doses of GBCAs have not developed NSF [5]. One study [18] described 30 patients who had an eGFR of under 30 ml/min/1.73 m² and who were exposed to high doses of gadodiamide (median dose of 90 ml and range of 40 to 200 ml). One of the 30 patients subsequently developed NSF, an observed incidence of about 3%.

Other possible risk factors

It is not understood why some patients with severe CKD or AKI develop NSF following exposure to GBCAs and others do not, but a number of possible co-factors have been postulated to play a role. These include metabolic acidosis or medications that predispose patients to acidosis [1,19]; elevated iron, calcium, and/or phosphate levels [19,20]; high-dose erythropoietin therapy [11]; immunosuppression [6]; vasculopathy [21]; and infection [22] or other acute pro-inflammatory events [4,23]. However, none of these have been consistently confirmed as true co-factors. As a result, routine screening for them prior to GBCA administration is not recommended, although such screening may be performed on an optional basis.

Hepatic insufficiency / hepatorenal syndrome

Initially, a number of researchers observed that a disproportionate number of affected patients had concomitant severe liver and renal dysfunction [4,5], prompting the FDA to warn against the use of GBCAs in patients with "...acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period" [24]. However, most data do not support this conclusion. For example, in one study, a review of the literature found that of 291 NSF patients, 34 (12%) had concomitant liver disease [25]; however, all but one of these patients also had known severe renal insufficiency (eGFR of <30 ml/min/1.73 m²) prior to GBCA administration. Thus, hepatic disease in and of itself, in the absence of AKI or severe CKD, is no longer considered a risk factor for NSF.

Postulated Mechanism

The exact mechanism of NSF causation is unknown. The most widely held hypothesis is that gadolinium ions dissociate from the chelates in GBCAs in patients with significantly degraded renal function due to the

prolonged clearance times of the GBCAs, as well as to other metabolic factors associated with this level of renal disease. The free gadolinium then binds with an anion such as phosphate, and the resulting insoluble precipitate is deposited in various tissues [9,26]. A fibrotic reaction ensues, involving the activation of circulating fibrocytes [26,27]. This hypothesis is supported by the greater presence of gadolinium in affected tissues of NSF patients relative to unaffected tissues [28]. Nevertheless, the detection of gadolinium in tissues is complicated and is not considered a requirement for diagnosis of NSF.

If the propensity for gadolinium to dissociate from various chelates is eventually proved to contribute to, or be primarily responsible for, the development of NSF, it may help explain, at least in part, why the various GBCAs differ in their apparent NSF safety profiles in at-risk patients [29].

Patients at Risk for NSF

Based on the above, the ACR Committee on Drugs and Contrast Media believes that patients receiving any GBCA should be considered at risk of developing NSF if any of the following conditions applies:

- on dialysis (of any form)
- severe or end-stage CKD (CKD 4 or 5, eGFR <30 ml/min/1.73 m²) without dialysis
- eGFR 30 to 40 ml/min/1.73 m² without dialysis*
- AKI [30,31]

*As further discussed below (see “Patients with CKD 3 [eGFR 30 to 59 ml/min/1.73 m²]”), patients with eGFR 30 to 40 ml/min/1.73 m² should also be considered at risk because eGFR levels may fluctuate (e.g., from the 30 to 40 ml/min/1.73 m² range one day to below <30 ml/min/1.73 m² on another day).

Identifying Patients at Risk for NSF Prior to Any GBCA Injection

It is important to identify patients at risk of developing NSF, as defined above, prior to any GBCA injection. The method used to identify such patients may differ for outpatients and inpatients.

Identifying At-Risk Outpatients

Regardless of the GBCA employed, outpatients should be screened for conditions and other factors that may be associated with renal function impairment. Simply asking patients if they have a problem with their kidneys is not considered an effective screening tool, as this has been shown to fail to detect many patients with chronic kidney disease, regardless of severity [32].

A more reliable method to identify outpatients who may have renal function impairment is to utilize a panel of questions that includes risk factors for compromised renal function. The following is a suggested list of risk factors that warrants pre-administration eGFR calculation in individuals scheduled to receive any GBCA injection. This list should not be considered comprehensive and represents a blend of published data [33,34] and expert opinion:

- Age >60
- History of renal disease, including:
 - o Dialysis
 - o Kidney transplant
 - o Single kidney
 - o Kidney surgery
 - o History of known cancer involving the kidney(s)
- History of hypertension requiring medical therapy
- History of diabetes mellitus

Many additional factors may have deleterious effects on renal function, including multiple myeloma, systemic lupus erythematosus, urinary tract infection, and some medications (e.g., non-steroidal anti-inflammatory drugs, diuretics, amino-glycosides, cyclosporine A, amphotericin, and others); however, the ACR Committee on Drugs and Contrast Media currently does not recommend routinely screening for these additional possible risk factors, since the incremental benefit in patient safety from such screening has not been established and is considered to be low by the Committee.

Once an outpatient is identified as being at risk for having reduced renal function based on screening, renal function should be assessed by laboratory testing (checking results of prior laboratory tests performed within an acceptable time window and ordering new laboratory tests only if necessary) and calculation of eGFR. However, if the patient is on dialysis, laboratory testing and calculation of eGFR is not useful.

For adults, eGFR calculation should be performed using the Modification of Diet in Renal Disease (MDRD) equation. The four-variable MDRD equation takes into account age, race, gender, and serum creatinine level. Commercially available point-of-service devices may facilitate this in an outpatient setting. The updated Schwartz equation should be used for children (also see Chapter on *Contrast Media in Children*).

MDRD equation:

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

Updated Schwartz equation:

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

A number of websites and point of service tools are available which can calculate eGFR values in adults and children.

When eGFR is recommended in Outpatients with Risk Factor(s) for Compromised Renal Function

There is no high-level scientific evidence to guide the time interval prior to GBCA injection with which an eGFR should be obtained in patients identified by screening to have one or more risk factor for compromised renal function. However, based on expert opinion and a need to maintain patient safety while minimizing the costs and burdens associated with additional laboratory testing, the ACR Committee on Drugs and Contrast Media recommends a new eGFR be obtained with the time intervals listed in the Chart below in outpatients who are identified by screening as at increased risk. The following guidelines are suggested: (See next page)

When a new eGFR should be obtained in outpatients with risk factor(s) for compromised renal function

Prior eGFR level (ml/min/1.73 m ²)	When was the last eGFR before MRI?	When should new eGFR be obtained prior to MRI?
None available	Not applicable	Within 6 weeks
>60	>6 months	Within 6 weeks
>60	<6 months (stable state*)	New eGFR not needed
>60	<6 months (possibly unstable state**)	Within 2 weeks
30–59	>2 weeks	Within 2 weeks
<30	>1 week	Within 1 week
On dialysis	Not applicable	New eGFR not needed

* = patient does not have a known condition that might result in acute deterioration of renal function

** = patient has a known condition that might result in acute deterioration of renal function. Such conditions include severe dehydration, febrile illness, sepsis, heart failure, recent hospitalization, advanced liver disease, abdominal surgery

If no risk factors for reduced renal function were identified at screening, new laboratory testing for eGFR does not need to be done.

Identifying At-Risk Inpatients

For all inpatients, eGFR level should be obtained within two days prior to any GBCA administration. In addition, the ordering health professional should assess inpatients for the possibility of AKI, as eGFR calculation alone has limited sensitivity for the detection of AKI.

General Recommendations for Imaging Patients at Risk for NSF

Once a patient at risk for NSF is identified, alternative diagnostic examinations that do not employ a GBCA should be considered. In nonemergent or nonurgent cases if the potential benefits of a GBCA-enhanced MRI are felt to outweigh the risk of NSF in an individual patient and there is no suitable alternative, the referring physician and patient should be informed of the risks of GBCA administration, and both should agree with the decision to proceed. In emergent or urgent cases it may not always be possible to inform the patient or referring physician prior to GBCA administration.

If the decision is made to administer a GBCA to a patient at increased risk for developing NSF, the supervising radiologist (including the name) should document the reason for the examination and the rationale for use of intravenous GBCA.

Group I agents (see [Table 1](#)), the GBCAs that have been most often associated with NSF, have been contraindicated by the FDA in these patients [24]. Alternative agents should be used.

The lowest possible dose of GBCA required to obtain the needed clinical information should be used, and it should generally not exceed the recommended single dose. (**Note:** the lowest diagnostic dose has not been thoroughly investigated for many indications and caution should be exercised so as not to administer a dose that is too low to provide the diagnostic information sought from the examination).

Exceptions to the above recommendation may be made at the discretion of the supervising radiologist, such as in the rare instance of an acute, life-threatening condition, and after consultation with the referring health care professional. However, the rationale for the exception must be documented by the supervising radiologist.

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

Additional Specific Recommendations for Specific Groups of Patients

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 MRI.

If a contrast-enhanced MR examination must be performed in a patient with end-stage renal disease on chronic dialysis, injection of group I agents (see [Table 1](#) at end of Chapter) is contraindicated. Also, use of the lowest possible dose needed to obtain a diagnostic study is recommended and is appropriate. The ACR Committee on Drugs and Contrast Media also recommend that GBCA-enhanced MRI examinations be performed as closely before hemodialysis as is possible, as prompt post-procedural hemodialysis, although unproven to date, may reduce the likelihood that NSF will develop. Because it may be difficult for a 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. Some experts recommend several dialysis sessions following GBCA administration, with use of prolonged dialysis times and increased flow rates and volumes to facilitate GBCA clearance.

Peritoneal dialysis probably provides less potential NSF risk reduction compared to hemodialysis and should not be considered protective.

Patients with CKD 4 or 5 (eGFR <30 ml/min/1.73 m²) not on chronic dialysis

The correct course of action in this patient group is problematic, as administration of iodinated contrast media for CT may lead to further deterioration of renal function, while administration of GBCA for MRI could result in NSF.

It is recommended that any GBCA be avoided in this patient group. However if GBCA enhanced MRI is deemed essential, use of the lowest possible dose needed to obtain a diagnostic study is recommended (note: for many MRI examinations, the lowest diagnostic dose has not been determined, and care should be taken not to lower the dose below diagnostic levels). Although there is no absolute proof that any GBCA is completely safe in this patient group, group I agents (see [Table 1](#) at end of Chapter) have been contraindicated by the FDA. Further, it may be prudent to avoid readministration of GBCA 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/1.73 m²)

NSF developing after GBCA administration to patients with eGFR >30 ml/min/1.73 m² is exceedingly rare. However, eGFR determinations may fluctuate from one day to the next (with an eGFR level just above 30 on one day changing to an eGFR below 30 on another day). It is for this reason that the precautions described above for CKD4 and CKD5 patients are also recommended for inpatients with an eGFR <40 ml/min/1.73 m². In comparison, no special precautions are required in patients with an eGFR of 40 to 59 ml/min/1.73 m² [36,37].

Patients with CKD 1 or 2 (eGFR 60 to 119 ml/min/1.73 m²)

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

Patients with acute kidney injury (AKI)

Patients with AKI who have been exposed to GBCA are at risk for developing NSF [15]. Due to the temporal lag between eGFR (which is calculated using serum creatinine values) and actual glomerular filtration rates, it is not possible to determine whether a given patient has AKI based on a single eGFR determination. Accordingly, caution should be exercised in use of GBCA in patients with known or suspected AKI regardless of measured serum creatinine or calculated eGFR values. GBCA should only be administered to these patients if absolutely necessary. When GBCA administration is required, agents associated with the greatest apparent NSF-associated risk (Group I agents, see [Table 1](#) at end of Chapter) should be avoided.

Children

At this time (August 2011) 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 demonstrate 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, however, that eGFR values in certain premature infants and neonates may be <30 ml/min/1.73 m² simply due to immature renal function (and not due to pathologic renal impairment). In these individuals, the ACR Committee on Drugs and Contrast Media believes that caution should still be used when administering GBCAs, although an eGFR value <30 ml/min/1.73 m² should not be considered an absolute contraindication to GBCA administration.

Caveat

Information on NSF and its relationship to GBCA administration is still evolving, and the summary included here represents only the most recent opinions of the ACR Committee on Drugs and Contrast Media (as of January 2012). 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.

Table 1

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

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

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

Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
Gadoteridol (ProHance® – Bracco Diagnostics)
Gadoteric acid (Dotarem® – Guerbet – as of this writing not FDA-approved for use in the U.S.)
Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)

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

Gadofosveset (Ablavar® – Lantheus Medical Imaging)
Gadoxetic acid (Eovist® – Bayer HealthCare Pharmaceuticals)

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

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