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CLINICAL UPDATE

Nephrogenic Systemic Fibrosis: What the Hospitalist Needs to Know

Derek M. Fine, MD[1]
Mark A. Perazella, MD[2]

[1] Department of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

[2] Section of Nephrology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

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Nephrogenic systemic fibrosis (NSF) has now been linked to gadolinium-based contrast (GBC) exposure in those with compromised kidney function, particularly those with end-stage renal disease (ESRD). When ESRD is present, symptoms can be quite devastating for the patient including severe pain and immobility and even death. For those at risk, avoidance of GBC exposure, whenever possible, is absolutely essential to prevent this potentially devastating complication. Identifying those at risk depends in some circumstances on appropriate recognition of renal dysfunction and understanding appropriate use of glomerular filtration rate (GFR) estimation formulas. Although hemodialysis (but not peritoneal dialysis) removes gadolinium, the availability of dialysis should never be used as a justification for GBC use in this high-risk population. Unfortunately there is a lack of a universally effective therapy. Resolution of acute kidney injury (AKI) appears to attenuate disease in most cases, while kidney transplantation has been associated with variable success. ***Journal of Hospital Medicine* 2010;5:46–50.** © *2010 Society of Hospital Medicine.*

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What Is Nephrogenic Systemic Fibrosis?

Nephrogenic systemic fibrosis (NSF) is a systemic fibrosing disease that occurs after exposure to gadolinium-based contrast (GBC) in the presence of severe renal failure of acute or chronic nature.[1,2–7] As suggested by its former name, nephrogenic fibrosing dermopathy, the cardinal feature of this disorder is skin involvement. Symptoms begin anywhere from 2 to 75 days after exposure to GBC, though usually within 2 months.[2–7] Initial signs and symptoms may include sharp and sometimes excruciating pain, tightening and burning of the skin associated with redness and swelling, symmetrical involvement, distribution with predilection for the extremities more than the trunk, and sparing of the face. The dependent lower extremities are more severely involved than the upper extremities. Dermal induration may occur in the form of plaques, nodules, and papules resulting in a "woody" texture on palpation. These findings usually progress over weeks to months with extensive dermal fibrosis involving entire limbs. Ultimately the patient may develop severe joint contractures and marked limitations in mobility.[8] A fulminant presentation is seen in approximately 5% of patients who develop a rapidly progressive course over as short a time period as 2 weeks.

Systemic organ involvement including fibrosis of the heart, lung, diaphragm, skeletal muscles, and other organs has been described and has been associated with fatal outcomes.[7–9]

Though more frequent in those with end-stage renal disease (ESRD), NSF has been seen in those with stage 4 and 5 chronic kidney disease (CKD) and acute kidney injury (AKI). Incidence rates have been difficult to calculate due to lack of exposure data in most studies, though 1 small case-control study found 4.3 cases per 1000 patient years among hemodialysis patients with an absolute risk of 3.4% in the exposed patient.[4] Interestingly, incident NSF rates published in a Centers for Disease Control case-control study of 19 NSF sufferers were much higher for peritoneal dialysis (4.6 cases/100 patients) than for hemodialysis (0.61/100 patients).[2] This is likely related to the different GBC clearance achieved with these modalities.

NSF has no predilection for gender, race, nationality or age group. Those with liver disease and lower body weight or lower muscle mass appear to be at greater risk, which may be related to overestimation of glomerular filtration rate (GFR) with falsely low creatinines seen in such patients. Risk is likely increased as well by multiple exposures to GBC in close proximity. Related host cofactors have not been identified, though elevated serum calcium and phosphate concentrations, exposure to high dose erythropoietin, and iron overload have been considered.[10,11]

The diagnosis of NSF requires compatible clinical findings along with consistent histopathology. Suspicious clinical findings in a patient with underlying kidney disease (AKI, CKD stages 4 and 5) who has been exposed to a GBC agent, should prompt skin biopsy. An incisional or deep punch biopsy to allow examination of dermis, epidermis and subcutaneous fat is required. The primary feature is the presence of collagen bundles with increased dermal spindle cells that stain for CD34 and procollagen I. Importantly, an inflammatory infiltrate is absent.[12,13]

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The major differential diagnosis includes scleroderma, eosinophilic fasciitis, morphea, scleromyxedema, and calcific uremic arteriolopathy. Scleroderma is distinguished by clinical findings such as facial involvement, Raynaud's phenomenon, and sclerodactyly with histology demonstrating normal or decreased numbers of fibroblasts on skin biopsy. Scleromyxedema is marked clinically by facial involvement, paraproteinemia on laboratory testing, and presence of inflammation sometimes seen on biopsy. Calcific uremic arteriolopathy (called calciphylaxis by some), which also occurs in those with kidney failure, is distinguished clinically by usually focal skin changes with cutaneous necrosis and ulceration and livedo reticularis; skin biopsy often reveals medial calcification of the vasculature with intimal fibrosis and luminal thrombosis.

What Is the Role of GBC in NSF?

The cause of NSF remained elusive for several years. Initially described in 2006 with several case series confirming the association, the role GBC agents in the pathogenesis of NSF gained widespread acceptance.[1,2–7] It should be noted that there are 5 cases of NSF described in kidney transplant patients where no exposure to Gadolinium was found.[14,15] Therefore, the possibility of other triggers remains.

The currently proposed pathogenesis needs to be understood in the context of gadolinium's pharmacologic properties. Gadolinium in its free ionic form (Gd^{3+}) is highly toxic and therefore is sequestered by a non-toxic organic molecule called a "chelate".[16,17] Dissociation of the Gd^{3+} from a chelate may occur through a process called transmetallation when the chelate binds with another endogenous metal such as zinc or copper, allowing the release of free Gd^{3+}. It is this free gadolinium that appears to be culpable in development of NSF.[18] GBC chelates can be categorized based on their biochemical structure (linear vs. macrocyclic) and their charge (ionic vs. non-ionic). Macrocyclic chelates bind Gd^{3+} more tightly than linear chelates and possess lower dissociation rates,[19] which may have implications for possible toxicity.

The prolonged half-life of GBC in the context of renal failure appears to predispose GBC to transmetallation and dissociation of Gd^{3+} from its chelate. Following intravenous injection, GBC is excreted unchanged by the kidneys via glomerular filtration. As a result, elimination half-life, which is approximately 1.6 hours in normal individuals, is increased approximately 4- to 33-fold in renal failure, depending on the level of GFR.[16,17,20,21] This increases the potential for Gd^{3+} dissociation through prolonged circulation times.

It has been postulated that once dissociated, deposition of the Gd^{3+} ion into skin and other organs sets off a cascade of poorly understood events that result in edema and fibrosis.[18] Recent findings of gadolinium deposition in the skin of patients with NSF as well as an animal model of NSF following GBC exposure support this hypothesis.[22–25] It appears that vascular trauma, endothelial dysfunction or transudation (edema) allows the Gd^{3+} metal to enter the tissues. This may explain the preponderance of initial symptoms in dependent areas of the limbs.

What Can Be Done to Prevent NSF?

Avoid GBC Exposure in at Risk Patients

GBC agents are contraindicated in those with ESRD, CKD with estimated GFR <30 mL/minute/1.73 m^2 (stages 4 and 5) and AKI. It has become common practice to use the 4-variable Modification of Diet in Renal Disease (MDRD) formula in estimating GFR.[26] Importantly, no estimating formula can be used in the context of a rising serum creatinine concentration as occurs with AKI. If a patient has AKI, one must assume a GFR <15 mL/minute until proven otherwise.

In those with low muscle mass the MDRD estimated GFR may overestimate the true GFR.[27] Therefore, the Cockcroft-Gault estimated creatinine clearance or a 24 hour urine-based creatinine clearance may be useful in identifying at risk patients with underlying CKD.

Choose the Lowest Risk GBC Agent

When GBC use is deemed necessary in the high risk individual, an agent with a macrocyclic chelate (gadoteridol in the United States) is recommended.[28] No published cases of NSF have been described with singular use of such agents. In addition, a retrospective study demonstrated no cases of NSF in ESRD patients on hemodialysis exposed to gadoteridol over a 7-year period.[29] This is not unexpected given the pharmacologic properties of this GBC agent.

Gadodiamide, a linear, non-ionic agent, appears to produce the greatest risk of NSF as the largest number of NSF cases has been reported with this agent. By October 2007, 283 of 447 cases reported to the Food and Drug Administration (FDA) were exposed to gadodiamide.[28] The significant preponderance with this agent is unlikely related to market share, reporting bias or publication bias. Gadopentetate, a linear, ionic agent, which had the greatest market share during this time, was responsible for approximately a quarter of cases reported to the FDA.[28] Based on these data, gadodiamide and gadopentetate (and probably all linear agents) should be avoided in high risk patients.

Use Lower Doses of GBC

The FDA approved dose of all GBC agents, except the macrocyclic agent gadoteridol, is 0.1 mmol/kg.[30] It appears that higher "off-label" doses of GBC agents (0.3-0.4 mmol/kg) which have been utilized for vascular studies (magnetic resonance angiography [MRA]), may have contributed to the emergence of NSF several years after these agents became available.

Develop a Protocol With Radiology and Nephrology Departments

Assessment of Renal Function Prior to Contrast Administration Is Required

Radiology departments should identify those with ESRD, CKD with estimated GFR <30 mL/minute/1.73 m^2 (stages 4

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TABLE 1. FDA-approved Gadolinium Contrast Agents

GBC Formulation	Year of Approval	Charge	Molecular Structure	Probable Risk of NSF*
Gadopentetate (Magnevist)	1988	Ionic	Linear	Medium
Gadoteridol (Prohance)	1992	Non-ionic	Cyclic	Very low
Gadodiamide (Omniscan)	1993	Non-ionic	Linear	High
Gadoversetamide (OptiMARK)	1999	Non-ionic	Linear	Medium
Gadobenate (MultiHance)	2004	Ionic	Linear	Low

Abbreviations: FDA, Food and Drug Administration; GBC: Gadolinium-based contrast; NSF, nephrogenic systemic fibrosis.
*Opinion based on summation of several references.[9,29,49,50]

and 5) and AKI. Using the 4-variable MDRD formula in estimating GFR with the caveats previously noted, radiology departments will identify most at-risk patients. Since the MDRD formula will be inaccurate in the setting of ESRD and AKI, these diagnoses should be determined through other means (for example, the patient's medical history) as part of the consent process.

Alternative Radiologic Imaging Modalities to GBC Enhanced Magnetic Resonance Imaging Should Be Utilized When Suitable in Those at High Risk

Newer techniques should be investigated as alternatives to GBC exposure. These include Magnetic Resonance Imaging (MRI) without GBC-enhancement, where options such as 3D time-of-flight MRA, phase-contrast angiography, and arterial spin labeling-MR provide excellent information about blood vessels and blood flow.[31] MRI with ultra-small paramagnetic iron oxide particles may offer a future alternative in those that need a contrast-based scan for diagnosis.[32]

However, since contrast enhanced MRI/MRA studies remain extremely important imaging modalities, their use may be required in some high risk individuals. In this circumstance, a macrocyclic chelate employed at the lowest dose possible, is recommended. The radiologist and nephrologist should be consulted in these instances.

Hemodialysis

Although hemodialysis efficiently clears GBC, its removal is not complete. Furthermore, it is not clear whether the damage has already occurred by the time a hemodialysis treatment can be instituted.[33] It should be recognized that GBC removal after one treatment averages 65% to 73.8%; 3 to 4 sessions are required to remove 99% of the contrast agent.[21,34] Peritoneal dialysis on the other hand is an ineffective method of GBC removal ($T_{1/2}$ of 52.7 hours).[21] Because not all of the circulating Gd^{3+} is removed with a single hemodialysis treatment, prolonged tissue exposure occurs in these patients. This is reflected by the development of NSF in patients despite undergoing consecutive hemodialysis treatments following GBC exposure.[3] Therefore, based on incomplete GBC removal with hemodialysis and the lack of evidence supporting prevention of NSF with this modality, we and others[33,35] strongly recommend avoidance of GBC in all patients with advanced kidney disease (GFR <30), regardless of the availability of hemodialysis. As such, the ability to perform hemodialysis after GBC in and of itself does not justify such exposure. However, if GBC use is deemed essential, then immediate hemodialysis should be strongly considered after exposure with further treatment on consecutive days.

TABLE 2. Treatment Possibilities in Nephrogenic Systemic Fibrosis*

Therapies most likely to benefit
Kidney transplant (in ESRD)
Physical therapy
Pain control
Therapies with anecdotal success
Extracorporeal photopharesis
Sodium thiosulfate
Therapies with limited success
Drugs: Glucocorticoids, Pentoxifylline, Cyclophosphamide, Thalidomide
Immunomodulatory: Plasmapharesis, Intravenous immunoglobulin
Local: Intralesional IFN-alpha, topical calcipotriene, other phototherapy

Abbreviations: ESRD, end-stage renal disease; IFN, interferon.
*Adapted from Linfert et al.[36]

Once NSF Develops, What Treatments Options are Available?

Unfortunately there is lack of a universally effective therapy for NSF. Several interventions have been described mainly in anecdotal case reports and very small case series. They have been recently reviewed (Table 2).[36]

Physical therapy is the mainstay of treatment for NSF. Physical therapy (and occupational therapy if needed) is essential to help prevent or slow the progression of joint contractures. Adequate pain relief, often with narcotics, is essential for patient comfort and to allow tolerance of physical therapy. Therapies with anecdotal benefit include extracorporeal photopheresis and infusions of sodium thiosulfate, a substance with chelating properties. Other interventions, such as immunosuppressive agents, topical agents and other phototherapies have shown limited success.

AKI resolution has been observed to result in regression of lesions.[1,37–40] Presumably, resolution of the AKI allows for clearance of gadolinium and other profibrotic mediators,

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TABLE 3. Strategies for Prevention of Nephrogenic Systemic Fibrosis

1. GBC agents are contraindicated in patients on dialysis regardless of availability of rapid treatment after exposure
2. Avoid MRI with GBC in those with GFR <30 ml/min (estimated by MDRD formula)
   MDRD formula may overestimate GFR in those of low weight—consider Cockcroft-Gault calculation or 24 hour urine collection for creatinine clearance
   MDRD is invalid in patient with a rising serum creatinine concentration. Assume GFR <30 in those with acutely rising serum creatinine concentration
3. Consider alternative imaging studies or MRI studies without Gadolinium – consult radiologist
4. If GBC study is a necessity, then as low a dose as possible of a macrocyclic chelate would be recommended
5. If an exposure to gadolinium occurs in ESRD, hemodialysis should be performed as soon as possible and repeated on consecutive days
6. If an exposure to gadolinium occurs in CKD 4 or 5 or AKI patient (not on dialysis), an individualized approach should be undertaken when considering temporary catheter placement and initiation of hemodialysis

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; GBC, gadolinium-based contrast; GFR, glomerular filtration rate.

though definitive evidence of this is not available. Based on the observed response to AKI recovery, it is not surprising that improvement after kidney transplantation has also been described.[1,41] However, responses have not been consistent.[39,42]

Consensus Guidelines and Recommendations

Nephrology societies have not yet developed consensus guidelines. Only the European Society of Urogenital Radiology has issued guidelines to date.[43] These guidelines are consistent with expert opinions published elsewhere and are reflected in our approach regarding prevention of NSF (Table 3).

The FDA has sent out several alerts since June 2006, the most recent in May 2007.[30,44–46] In its "Information for Healthcare Professionals" alert, the FDA outlines recommendations. These are included in our final recommendations shown in Table 3.[30] Those with a recent liver transplant, or those with chronic liver disease, who have associated kidney insufficiency of any severity, have also been identified by the FDA as an at risk group. This is based on reports of NSF occurring more commonly in patients with AKI who have these underlying conditions.[47]

Conclusions

With the high and increasing rates of AKI, CKD and ESRD seen among hospitalized patients,[48] the need for vigilance when obtaining imaging with GBC agents becomes particularly important in the inpatient setting. As a preventable disease, it is incumbent upon us to fully understand the risk factors and potential pitfalls that may result in a patient exposed to these agents. The hospitalist has the unique role of acting as a firewall between the patient and the imaging study that may put him or her at risk for this devastating disorder.

Identification of GBC as a major culprit in the development of NSF and hence avoidance of this agent in those at the highest risk is expected to reduce the incidence of NSF. It is likely that the future will bring further understanding of the underlying mechanisms of gadolinium-induced NSF and with this understanding, even safer strategies for GBC usage. However, until safer contrast agents become available, avoidance of GBC exposure in those with advanced acute or CKD remains our most important defense.

Address for correspondence and reprint requests:
Derek M. Fine, 1830 East Monument Street; Suite 416; Baltimore, MD 21205; Telephone: 410-955-5268; E-mail: dfine1@jhmi.edu Received 3 March 2008; revision received 26 December 2008; accepted 7 January 2009.

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