

**CLINICAL REVIEW**

# Nephrogenic Systemic Fibrosis and Its Association with Gadolinium-Containing MRI Contrast Agents

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**ABSTRACT**

Nephrogenic systemic fibrosis (NSF) is a potential high-risk adverse drug reaction to gadolinium, the main contrast agent used in magnetic resonance imaging (MRI). With the ever increasing demand and applications of MRI, MR angiography and contrast-enhanced MRI, health care professionals should be aware of this potentially serious entity. The etiology of NSF, clinical implications, method of diagnosis and treatment options of NSF will be reviewed in the present paper. An emphasis will be placed on the theorized pathogenesis and comparison of the different gadolinium-containing contrast agents available in Canada and the United States. Additionally, a proposed algorithm for identifying susceptible patients and stratifying them by their risk of developing NSF will be discussed. As no proven therapy for the treatment of NSF currently exists, it is imperative that efforts be directed at prevention by minimizing exposure of high risk patients to gadolinium.

**INTRODUCTION**

**N**ephrogenic systemic fibrosis (NSF) is an emerging disorder that results in widespread tissue fibrosis, occurring exclusively in patients with renal impairment. It was previously termed nephrogenic fibrosing dermopathy when first recognized in 1997. Over time, it has been demonstrated that this disorder causes systemic fibrosis in various organs throughout the body.<sup>3-6</sup> Since it was first described in 2000, over 215 cases have been reported to the registry at Yale University, run by Dr. Shawn Cowper.<sup>1,7</sup> Although NSF is a relatively rare disease with an approximate incidence rate of 0.0043 per 100 patient-years, it can be severely debilitating and may lead to death.<sup>3</sup>

Gadolinium, the most commonly used magnetic resonance imaging (MRI) contrast agent, has been associated with the development of this disorder. The gadolinium ion has unpaired electrons, rendering it paramagnetic and hence a useful contrast agent in MRI. As free gadolinium ions are toxic, the ion is chelated to a variety of vendor-specific ligands which render it suitable for intravenous administration. As with other contrast media, the goal of a gadolinium-enhanced MRI is to highlight differences between normal and abnormal tissue. It can demonstrate areas of blood-brain barrier breakdown in the central nervous system, help char-

acterize pathology by the pattern of perfusion and enhancement (or lack thereof), and can be used to augment signal in vessels for the purposes of MR angiography and MR venography. With the rapidly-growing indications for, and applications of, contrast-enhanced MRI, it is imperative that guidelines be established with regards to gadolinium administration to minimize the incidence of NSF.

**ETIOLOGY**

Multiple theories have been postulated regarding factors that confer susceptibility to NSF, although no proven cause-effect relationship currently exists. Current theories include renal dysfunction, high dose gadolinium administration, tissue injury, proinflammatory conditions and hypercoagulable states.

NSF occurs in the setting of patients with severe renal dysfunction that undergo magnetic resonance imaging with gadolinium-containing contrast agents. Two observational studies found that the odds ratio for developing NSF among those exposed to gadolinium versus those that were not exposed to be 22.3 and 32.5.<sup>8,9</sup> Approximately 90% of patients that contract NSF are dialysis-dependent.<sup>10</sup> Typically, patients with glomerular filtration rates (GFRs) less than 30 mL/min/1.73 m<sup>2</sup> are at risk although, according to

Sadowski and colleagues' findings, even patients with GFRs less than 60 mL/min/1.73 m<sup>2</sup> are susceptible, particularly if hospitalized with a proinflammatory condition.<sup>11,12</sup> An additional subset of patients that appear to be at risk are those in the perioperative liver transplantation period.<sup>11,13,14</sup>

There also appears to be a dose-response relationship where patients receiving 0.2 mmol/kg of gadolinium had a 12.1-fold higher risk of developing NSF than those exposed to the standard dose of 0.1 mmol/kg.<sup>9</sup> Of the seven major gadolinium-containing contrast agents approved in Canada and the United States, high doses of Omniscan (gadodiamide) appears to be associated with the greatest number of cases (Table 1). Unfortunately, even gadodiamide doses as low as 0.11 mmol/kg have been associated with NSF.<sup>12,15</sup> Although this strong connection between gadolinium administration and the onset of NSF exists, the absolute risk for a patient with end-stage renal disease receiving gadolinium and subsequently contracting NSF is only approximately 3.4%.<sup>3,16</sup>

Many other factors have been implicated in increasing one's susceptibility to acquiring NSF, including hypercoagulability, metabolic acidosis, erythropoietin administration and surgical or vascular interventions.<sup>3,5,17-21</sup> The voluntary NSF registry confirms a trend that most patients have experienced some form of tissue injury approximately two weeks prior to the development of NSF.<sup>7</sup> These commonly include major surgery or a vascular event such as thrombosis. A proinflammatory event had occurred in all 13 patients in Sadowski and colleagues' paper and eight of 12 patients in Broome and colleagues' paper.<sup>8,12</sup>

## PATHOGENESIS

Several hypotheses exist regarding the sequence of biological events that occur following gadolinium administration that lead to the development of systemic fibrosis. Renal disease is clearly the ubiquitous and key player in what is likely a multifactorial and multi-step cascade resulting in NSF. The half-life of administered gadolinium is increased due to impaired renal clearance, thereby increasing the chance of the toxic gadolinium ion dissociating from its ligand and depositing in tissues. Inflammation or tissue injury appears to have a two-fold deleterious effect in the development of NSF. First, endothelial damage likely promotes free gadolinium ion entrance into the tissue and second, may cause cytokine release that leads to the recruitment of circulating fibrocytes, cells normally involved in wound repair.<sup>2</sup> Macrophages drawn to the injured tissues are presumed to phagocytose the gadolinium ion, resulting in release of profibrotic cytokines which further exaggerate scar formation.<sup>22</sup> This theory is strengthened by the discovery of gadolinium deposition in skin biopsies of patients with NSF.<sup>23,24</sup> Furthermore, erythropoietin has been suggested to play a role in the onset of NSF in some cases.<sup>19,25</sup> Its profibrogenic potential upregulates the production of circulating fibrocytes and subsequently exaggerates the wound healing response.

Four major manufacturers have produced gadolinium-containing contrast agents in North America (Table 1). Because free gadolinium is toxic, these manufacturers

**Table 1.** Gadolinium containing contrast agents: Comparing association with NSF and agents' stability

Brand Name	Year of implementation <sup>15</sup>	Percentage of associated cases of NSF (as of August 2007) <sup>29,43</sup>	Excess chelate content (mg/mL)	Standard dose (mL/kg)*	Standard dose (mmol/kg)	Molecular structure <sup>15</sup>	Conditional (C) and Thermodynamic (T) stability constants <sup>15</sup> (log K <sub>eq</sub> )	Acid dissociation rate <sup>15</sup> k(obs')s <sup>-1</sup>
Omniscan© (gadodiamide)	1993	87.2	12	0.1-0.2**	0.1	Linear, nonionic	C=14.9 T=16.9	<2x10 <sup>-2</sup>
OptiMARK© (gadoversetamide)	1999	1.8	28.4	0.2	0.1	Linear, nonionic	C=15.0 T=16.6	Unavailable
MultiHance© (gadobenate dimeglumine)	2004	0	0.1	0.2	0.1	Linear, ionic	C=18.4 T=22.6	Unavailable
Vasovist© (gadofosveset trisodium)	2006	0	Unavailable	0.12	0.03	Linear, ionic	Unavailable	Unavailable
Magnevist© (gadopentetate dimeglumine)	1988	10.0	0.4	0.2	0.1	Linear, ionic	C=18.1 T=23.8	1.2x10 <sup>-3</sup>
ProHance© (gadoteridol)	1992	0.9	0.23	0.2	0.1	Macrocyclic, nonionic	C=17.1 T=23.8	6.3x10 <sup>-5</sup>
Gadovist© (gadobutrol)	2004	0	0.513	0.1-0.3**	0.1	Macrocyclic, nonionic	Unavailable	Unavailable

\*More than double the standard dose may be required for specific studies (i.e., magnetic resonance angiography, perfusion studies, etc.).

\*\*Depends on what component of the body is being imaged.

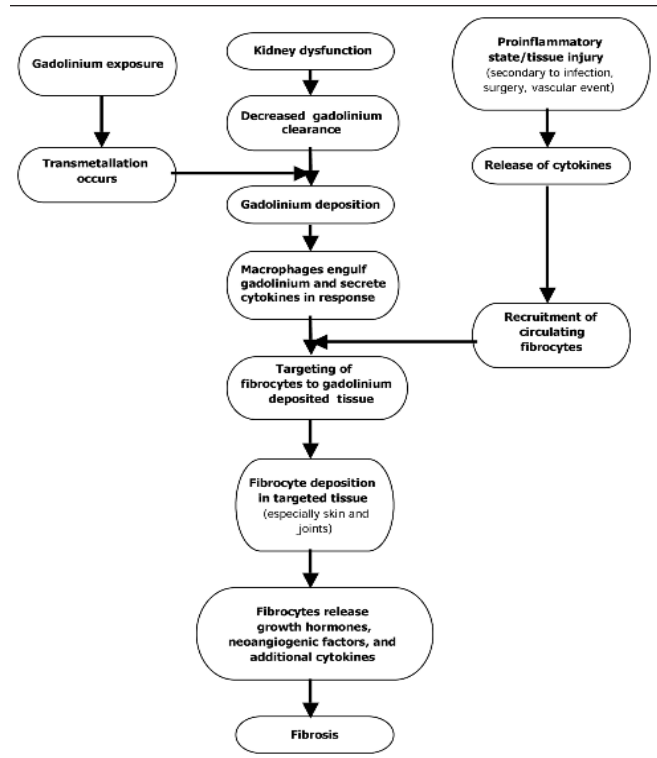
chelate gadolinium with ligands that are specific to their company. In order to decrease the amount of gadolinium ions dissociating from the chelate, the manufacturers added excess ligand in an effort to “mop up” free gadolinium. This results in a significant increase in the LD50’s (the dose that is lethal to half of the animals tested) of the gadolinium-chelate complexes.<sup>26</sup> Marckmann and colleagues hypothesized that the excess chelate might contribute to the onset of NSF, although it is considerably more likely that it has a protective effect by binding free gadolinium.<sup>8,9</sup>

Various proposals have been put forth to explain why certain gadolinium-containing contrast agents, such as gadodiamide (Omniscan), are associated with more cases of NSF than others. Some of these include the chelate’s molecular structure, the stability of the gadolinium-chelate structure, and the acid dissociation rate (i.e., how quickly the structure breaks down in the face of sufficient energy). There are four major ways a chelate can bind the gadolinium ion. Listing these in order of weakest to strongest affinity for the gadolinium ion are as follows: non-ionic linear (e.g., Omniscan and Optimark), ionic linear (e.g., Magnevist and MultiHance), and ionic and non-ionic macrocyclic (e.g., Gadovist and ProHance) agents. Transmetallation, the release of free gadolinium from chelate and the subsequent binding to endogenous ions, occurs more readily in chelates having a weaker affinity for gadolinium such as those that demonstrate non-ionic linear bonding.

Preclinical trials in rats exposed to high levels of various gadolinium-containing agents reveal several fascinating results.<sup>27</sup> First, many rats developed skin lesions compatible with NSF and the number of skin lesions correlated with skin concentration of gadolinium, clearly implicating gadolinium as the responsible toxin. Furthermore, *in vitro* thermodynamic stabilities were clearly shown to have an *in vivo* effect in these rats. Agents with low stability (e.g., Omniscan) were associated with the highest concentrations of gadolinium in the skin and development of the most skin lesions. Ionic linear chelates and macrocyclic agents with higher stabilities had considerably lower concentrations of gadolinium in the skin and no macroscopic lesions to suggest NSF.

Metabolic acidosis secondary to renal impairment has been suggested to be involved in the pathogenesis of NSF; however, it does not appear to be a necessary precursor to the development of this disease as demonstrated by three patients in Marckmann and colleagues’ study.<sup>9,18</sup> If it does play a role, High and colleagues suggested that it may alter the gadolinium-carrier complex dissociation constant or may negatively impact clearance of these substances from the body.<sup>24</sup>

By combining existing hypotheses and drawing conclusions from the available data, the authors have constructed a more complete hypothesis than is yet available in the current literature for the pathogenesis of NSF (Figure 1).



**Figure 1.** Proposed pathogenesis of nephrogenic systemic fibrosis (NSF).

## MANIFESTATIONS

Nephrogenic systemic fibrosis, as the name implies, causes widespread fibrosis impacting both the skin and internal organs. Clinical signs develop over days to several weeks; however, progression is quite variable between patients.<sup>7,23</sup> Externally, it classically progresses from swelling of the hands and feet to skin thickening with a peau d’orange appearance.<sup>30</sup> Erythematous indurated plaques or confluent areas of fibrosis typically present symmetrically with the skin becoming tight and having a woody texture over time.<sup>8</sup> The skin is affected starting with the extremities, with a propensity for the areas between the ankles and thighs, possibly progressing to the trunk and buttocks.<sup>7,23</sup> Typically the head and neck are spared. This provides one of the major differentiating factors from scleroderma, a disorder that has a close clinical resemblance. In addition to the classic plaques of NSF described earlier, some patients have noted yellow plaques or papules on or near the eyes.<sup>7</sup> NSF may also lead to fibrosis of skeletal muscle, myocardium, pericardium, diaphragm, lung parenchyma, pleura, esophagus, liver, testes, kidney, bone and dura.<sup>3-6</sup> Skeletal muscle involvement can lead to symptoms of weakness.<sup>8</sup> Rapid, new onset fluctuating hypertension has been described prior to onset of skin lesions.<sup>7</sup> Over time, as the fibrosis worsens, NSF can cause immobility and joint contractures.<sup>16</sup> Accompanying these symptoms, patients may complain of limited range of motion, arthralgias, myalgias, paresthesias, and/or severe pruritus.<sup>8,31</sup>

## DIAGNOSIS

Skin biopsy sufficient to sample the dermis, subcutaneous fat and fascia is the gold standard diagnostic technique for NSF.<sup>8</sup> Histological analysis of the sampled tissue will display different appearances depending on the age of the lesion.<sup>23</sup> Early lesions show mildly increased production of spindled fibroblasts with small amounts of collagen. Older lesions demonstrate very high levels of spindled fibroblasts and collagen in the dermis and subcutis. As mentioned, the gadolinium ion is sometimes isolated from skin biopsies in affected patients.

No blood tests are pathognomonic for NSF, but C-reactive protein and erythrocyte sedimentation rate may be elevated.<sup>30</sup> This is possibly secondary to the proinflammatory state (i.e., recent major surgery or vascular event) that many NSF patients have prior to gadolinium exposure.

## TREATMENT

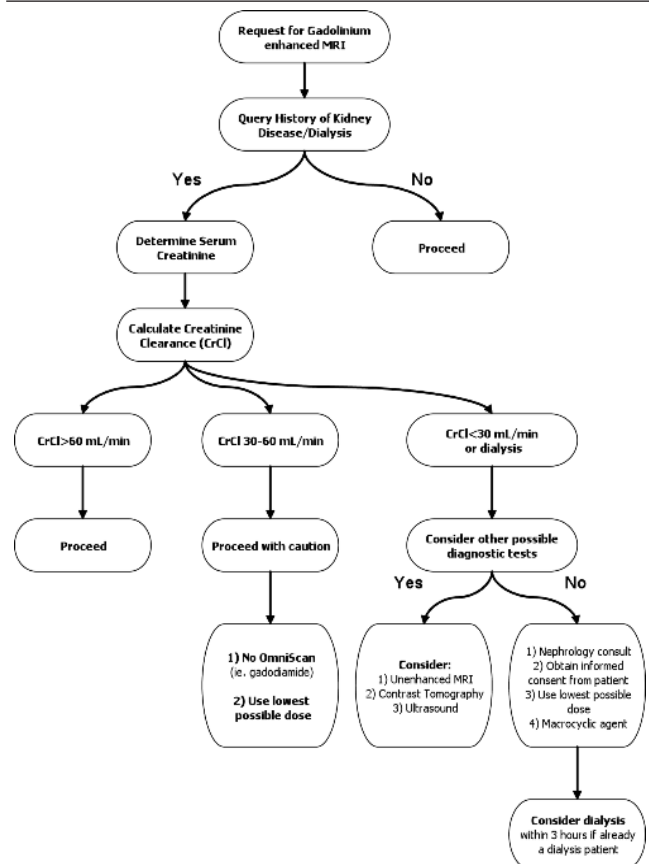
Multiple treatment modalities to prevent new cases or to improve existing cases of NSF have been tried with varying degrees of success. No standard of care currently exists for this disease. The complex nature of the disease as well as the multiple comorbidities that exist in patients presenting with NSF make finding a treatment very difficult.

Since the average excretory rates of gadolinium after the first, second, third, and fourth hemodialysis sessions are 78.2%, 95.6%, 98.7% and 99.5% respectively, the U.S. Food and Drug Administration (FDA) has recommended in their most recent advisory in 2007 to “consider prompt hemodialysis after administration of a gadolinium-based contrast agent” in susceptible patient populations already requiring hemodialysis, with the goal of NSF prevention.<sup>32,33</sup> It is generally accepted that dialysis should be conducted in the first three hours after gadolinium exposure.<sup>34</sup> Unfortunately, no clear evidence proves that dialysis decreases the occurrence of NSF. In fact, Broome and colleagues demonstrated in a study of 12 patients that prompt dialysis did not appear to prevent the development of NSF.<sup>8</sup> As a result, susceptible patients not already on dialysis should not undergo dialysis after gadolinium exposure.

Several patients diagnosed with NSF have shown significant improvement with a return to normal kidney functioning after successful kidney transplantation, although others have had no improvement in their clinical signs.<sup>7</sup> Multiple other methods have been attempted in treating NSF including plasmapheresis, pentoxifylline, extracorporeal photopheresis, physical therapy, oral corticosteroids, ultraviolet therapy, intravenous sodium thiosulfate, immunoglobulin therapy, topical dovonex and thalidomide.<sup>7,15,18,30,35-40</sup> Unfortunately, these techniques have demonstrated variable success with improvement only noted in anecdotal reports.

Because there are no proven therapies for treating NSF, the focus must be shifted to prevention. Patients with renal

impairment needing contrast-enhanced MRI should be carefully selected such that the benefit does not outweigh the possibility of harm. Broome and colleagues suggest a screening measure that may be useful. It involved obtaining a recent serum creatinine and calculated creatinine clearance if a patient is receiving a gadolinium contrast agent and has a history of kidney disease or diabetes mellitus or if the patient is older than 60 years.<sup>8</sup> This strategy may identify susceptible candidates and thereby avert disease onset. A proposed algorithm is detailed in Figure 2. These recommendations are in line with the FDA’s most recent guidelines (May 2007): in patients with severe renal compromise (GFR less than 30 mL/min/1.73 m<sup>2</sup>) or recent hepatic transplantation needing to be imaged, alternate methods (i.e., non contrast MRI, CT, ultrasound, etc.) should be considered.<sup>33</sup> Metabolic acidosis in patients with renal impairment is a probable precursor to the disease and as a result should be aggressively corrected in all patients likely to need gadolinium-enhanced MRI.<sup>18</sup> If gadolinium-containing contrast is administered, use the lowest effective dose, as was suggested by the European Society of Urogenital Radiology, and avoid the use of gadodiamide (Omniscan) specifically.<sup>41</sup> Furthermore, patients already on routine dialysis should undergo immediate hemodialysis following contrast injection.<sup>33</sup>



**Figure 1.** Nephrogenic systemic fibrosis (NSF) prevention algorithm.

## PROGNOSIS

NSF has a variable prognosis; while it can improve slightly, spontaneous remission has not been reported.<sup>7</sup> Mortality rates of patients with NSF are increased over that of the general population. Typically, it is not the cause of death but can predispose to related comorbidities that ultimately result in patient demise. For example, NSF can result in diminished ventilation via diaphragmatic fibrosis or can hinder mobility such that the patient suffers a life-threatening fall. Deo and colleagues' study of three patients with NSF demonstrated a mortality rate of 67%.<sup>3</sup> Sadowski and colleagues reported a mortality rate of 31% (4 of 13 patients), although not all deaths appeared as a direct result of NSF (acute respiratory distress syndrome, sepsis with respiratory failure, respiratory failure due to esophageal rupture, and cardiac arrest due to ventricular fibrillation).<sup>12</sup>

## CONCLUSION

NSF is a rare but potentially fatal condition affecting a specific subpopulation. Most evidence indicates it is an adverse drug reaction to gadolinium primarily in dialysis-dependant patients, but non-dialyzed patients with severe renal dysfunction are also at risk. Given the lack of effective therapy and its potentially severe manifestations, efforts should be focused on disease prevention. Additionally, it is imperative that all new cases are reported to Health Canada or the U.S. FDA and the NSF registry in an attempt to achieve a better understanding of this complex disease.

In response to recent research findings, Dr. Kuo of Yale University, working in conjunction with Dr. Cowper at the NSF registry, stated that contrast-enhanced MRI is the best examination in many situations and excluding large numbers of patients with severe renal failure from the best test may cause more harm than good.<sup>42</sup> In many instances, the benefits of a confident diagnosis with a contrast-enhanced MRI outweighs the potential risks of NSF development. The estimated risk of NSF after receiving a dose of gadolinium in severe renal impairment is less than 4%. This risk can further be minimized by decreasing dose and avoidance of unstable non-ionic linear chelates such as Omniscan. Certainly, the risk of NSF is not uniform amongst the various gadolinium chelates, with in vitro and preclinical studies suggesting macrocyclic agents may be a safe alternative. There is a strong need for well-designed multi-centre trials to confirm this theory. By taking a balanced approach to imaging amongst this subset of patients, one can attempt to identify those at the highest risk and consider alternate modalities or modification of existing factors.

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