Nephrogenic systemic fibrosis: A systemic fibrosing disease resulting from gadolinium exposure

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Nephrogenic systemic fibrosis (NSF) is an iatrogenic fibrosing disorder that primarily affects individuals with chronic kidney disease (CKD) following exposure to gadolinium-based contrast agents (GBCAs) during imaging procedures. NSF is characterised by skin thickening, tethering and hyperpigmentation; flexion contractures of joints; and extracutaneous fibrosis. This article reviews the history, clinical manifestations, epidemiology, histopathology and pathophysiology of this disabling disease.

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How was NSF first recognised?

NSF was first observed in 1997 at Sharp Memorial Hospital in San Diego, California. Between May 1997 and November 2000, 8 of 265 renal transplant recipients at that hospital developed flexion contractures, hyperpigmentation and ‘brawny induration’ of their skin [1]. In 2000, 14 patients with stage 5 CKD who developed a scleromyxoedema-like skin disease, but without facial involvement or circulating paraproteins, were described in a published case series [2]. Dermatopathologists at the University of California, San Francisco, analysed skin biopsies from these patients and noted a novel histopathologic appearance that was distinct from scleromyxoedema and other known fibrosing diseases [3]. In 2001, this scleromyxoedema-like skin disease was termed nephrogenic fibrosing dermopathy (NFD) [3]. NFD was later renamed nephrogenic systemic fibrosis (NSF), when involvement of tissues other than skin was recognised [4].

What are the clinical manifestations of NSF?

NSF typically presents with rapidly progressive skin thickening, tethering and hyperpigmentation, principally involving the extremities [2]. Skin changes usually appear first on the distal lower legs and feet and then progress cephalad to involve the thighs, hands, forearms and upper arms. The skin on the chest, abdomen and back is affected much less often than that on the extremities.

Early in the course of NSF, affected skin may be erythematous and oedematous, lacking hyperpigmentation. These early skin lesions may be pruritic and can be mistaken for an allergic reaction. As cutaneous fibrosis progresses, however, the skin becomes significantly indurated and tethered to the point where it cannot be pinched. It commonly appears shiny with brawny hyperpigmentation (Fig. 1). These established skin lesions are typically extremely painful.

Patterned plaques are another cutaneous manifestation of NSF. These thin, fixed plaques are red to violaceous in colour and have a polygonal or reticular appearance [5]. Patients may also have superficial, hypopigmented pink or flesh-coloured macules with irregular borders that eventually coalesce into patches or thin plaques [5]. Later in the course of NSF, patients may develop epidermal atrophy and hair loss, follicular dimpling (peau d’orange), ‘cobblestoning’, and hyperkeratosis with scaling [6].

Patients with advanced NSF commonly develop flexion contractures of the fingers, elbows and knees as a result of periarticular skin tightening (Fig. 2). These flexion contractures can severely impair physical
function [7]. Patients may also develop extracutaneous fibrosis of skeletal muscle, diaphragm, lymph nodes, heart, lungs, pleura, oesophagus, liver, thyroid, genitourinary tract, sclera and dura mater [8–12].

What is the differential diagnosis of NSF?

First and foremost, the clinician must suspect that a patient may have NSF. NSF is a clinical diagnosis that can be misidentified as one of several other fibrosing disorders, including scleromyxoedema, scleroderma diabetica and diffuse cutaneous or limited cutaneous systemic sclerosis (Table 1). There are, however, several important clinical and historical features that aid the clinician in distinguishing NSF from other fibrosing disorders. A key clinical feature that distinguishes NSF from systemic sclerosis and scleromyxoedema is the nearly universal absence of facial skin involvement in NSF [2]. Moreover, patients with NSF may have slightly raised, yellow plaques on the sclera of their eyes, adjacent to the iris, that are often accompanied by conjunctival injection [13] (Fig. 3). Raynaud’s phenomenon, periungual capillary dilatation and dropout and telangiectasias, which are commonly present in patients with systemic sclerosis, are not features of NSF. In addition, patients with NSF do not develop acroosteolysis.

Fig. 2. Periarticular skin tightening causing flexion contractures of the fingers and elbows of a patient with nephrogenic systemic fibrosis.
<table>
<thead>
<tr>
<th>Fibrosing disorder</th>
<th>Clinical and historical features</th>
<th>Laboratory assessment and studies, if applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipodermatosclerosis / chronic venous stasis</td>
<td>Lesions of induration/dyspigmentation typically confined to the leg below the knee, without joint contractures. Varicosities present proximal to lesions of induration.</td>
<td>Venous duplex ultrasound with reflux testing.</td>
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<tr>
<td>Scleromyxedema (lichen myxoedematous)</td>
<td>Numerous, minute (2–3 mm), firm, closely spaced papules on hands, arms, upper aspect of trunk, and/or face and neck. Papules often arranged in linear pattern. May show glabellar furrowing.</td>
<td>Serum protein electrophoresis and serum immunofixation or immunoelectrophoresis for monoclonal gammopathy.</td>
</tr>
<tr>
<td>Systemic sclerosis (limited cutaneous and diffuse cutaneous)</td>
<td>Limited form with cutaneous involvement limited to face and skin distal to elbows and knees. Diffuse form with cutaneous involvement that includes extremities proximal to elbows and knees as well as trunk. May show diffuse hyperpigmentation or salt/pepper dyspigmentation (sparing or hypopigmentation around hair follicles) of forehead or in shawl distribution on trunk. Sclerodactyly. More likely to show induration of areas not typical of NSF (trunk and face, decreased oral aperture). Periungual dilated capillary loops. Raynaud’s phenomenon. Telangiectasias. Ischaemic and traumatic digital ulcerations. Acral osteolysis.</td>
<td>Antinuclear antibody titre and pattern. Anti-centromere antibodies. Anti-topoisomerase 1 (Scl-70) antibodies. Anti-RNA polymerase III antibodies. Nailfold capillaroscopy.</td>
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<tr>
<td>Scleredema diabeticorum</td>
<td>Primarily involves upper aspect of back with induration/erythema.</td>
<td>Serum glucose (fasting). Haemoglobin A1c.</td>
</tr>
<tr>
<td>Morphea / lichen sclerosis et atrophicus</td>
<td>Linear or guttate lesions of induration/dyspigmentation, typically paucilesional and asymmetric.</td>
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<tr>
<td>Chronic graft-versus-host disease</td>
<td>More likely to show lichenoid papules, erosive indurated plaques. Involvement of trunk.</td>
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<tr>
<td>Pruritus of renal disease / neuropathy</td>
<td>Lesions primarily secondary to chronic scratching, e.g., erosions/ulcers.</td>
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<tr>
<td>β2-Microglobulin amyloidosis</td>
<td>More likely to exhibit subcutaneous masses around shoulders and wrists and on palms of hands, without cutaneous lesions.</td>
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</tbody>
</table>
Laboratory testing may support a clinical diagnosis of NSF by demonstrating the absence of antibodies that are present in some patients with other fibrosing disorders. Autoantibodies, such as antinuclear antibodies, anti-centromere antibodies, anti-topoisomerase I (Scl-70) antibodies and anti-RNA polymerase III antibodies may be present in patients with systemic sclerosis but are usually absent in patients with NSF. The absence of a circulating paraprotein can help to distinguish NSF from scleromyxoedema.

Table 1 (continued)

<table>
<thead>
<tr>
<th>Fibrosing disorder</th>
<th>Clinical and historical features</th>
<th>Laboratory assessment and studies, if applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiff skin syndrome / congenital fascial dystrophy</td>
<td>Childhood onset Buttocks and thighs with bound-down skin Contractures of knees and hips commonly Hypertrichosis over involved areas Sharp demarcation at inguinal crease</td>
<td>Tense, photodistributed bullae and vesicles Subtle facial hypertrichosis Shiny, firm, bound-down plaques of photoexposed and unexposed skin</td>
</tr>
<tr>
<td>Sclerodermoid porphyria cutanea tarda</td>
<td>Tense, photodistributed bullae and vesicles Subtle facial hypertrichosis Shiny, firm, bound-down plaques of photoexposed and unexposed skin</td>
<td>Caused by ingestion of l-tryptophan contaminated with 1,1'-ethyldienebis-l-tryptophan</td>
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</table>


Laboratory testing may support a clinical diagnosis of NSF by demonstrating the absence of antibodies that are present in some patients with other fibrosing disorders. Autoantibodies, such as antinuclear antibodies, anti-centromere antibodies, anti-topoisomerase I (Scl-70) antibodies and anti-RNA polymerase III antibodies may be present in patients with systemic sclerosis but are usually absent in patients with NSF. The absence of a circulating paraprotein can help to distinguish NSF from scleromyxoedema.

![Fig. 3. A yellow scleral plaque, adjacent to the iris, accompanied by conjunctival injection. Reproduced with permission from Bernstein EJ. Kay J. Nephrogenic systemic fibrosis: A fibrosing disorder induced by gadolinium exposure. Int J Adv Rheumatol 2011;9(4):123–33.]](image_url)
Which patients are at risk for developing NSF?

Grobner first posited an association between NSF and GBCA exposure in 2006, when he observed five of nine haemodialysis patients develop skin changes of NSF within 2–4 weeks after receiving an intravenous infusion of gadodiamide (Omniscan®) [14]. Since this landmark publication, several studies have confirmed the association between administration of GBCA to individuals with CKD and the subsequent development of NSF (Table 2) [15–22]. This association fulfils most of the Bradford-Hill criteria for causality [23,24] (Table 3). Although multiple and higher cumulative doses of GBCA confer an increased risk of developing NSF, this fibrosing disorder can develop after only a single dose of a GBCA [22].

The majority of NSF cases have been identified in patients with stage 5 CKD who were receiving chronic haemodialysis. Among several retrospective studies published in 2007, the estimated prevalence of NSF among patients with stage 5 CKD ranged from 0.5% to 6% [16,17,25,26]. However, in a cross-sectional study of haemodialysis patients in Massachusetts that was also published in 2007, skin changes characteristic of NSF were identified in 25 of 186 patients (13%) with stage 5 CKD [15]. In this study, prior exposure to a GBCA was strongly associated with the subsequent development of skin changes of NSF, with an odds ratio of 14.7. Sixteen of 54 patients (30%) with known prior exposure to gadopentetate dimeglumine (Magnevist®) demonstrated skin changes of NSF [15]. In a retrospective cohort study that was published the following year, 18 of 190 (10%) CKD patients in Denmark who had been exposed to gadodiamide (Omniscan®) had evidence of NSF by history, physical examination and histological examination of tissue [27]. All 18 patients with NSF had stage 5 CKD. Thus, in this cohort, the prevalence of NSF among the 102 patients with stage 5 CKD was 18%.

Although other retrospective series have reported a lower prevalence of NSF, the types of patients included in many of these reports are quite variable (Table 2). Some studies, for example, do not limit inclusion to patients with stage 5 CKD and instead include as the denominator all patients exposed to a GBCA, regardless of CKD status. Moreover, in most of these studies, patients were not examined by the investigators for the presence or the absence of clinical features of NSF. Instead, the authors relied on documentation of the presence of NSF in a patient’s chart and equated the absence of such documentation with the non-existence of NSF. Given that the clinical features of NSF are not always actively sought by health-care professionals evaluating patients with stage 5 CKD who have been exposed to GBCA, one cannot rely on passive reporting of cases to determine the true prevalence of NSF.

Several studies illustrate this point. In a retrospective cohort study of 61 patients with stage 3, 4 or 5 CKD who had received high-dose gadodiamide for catheter angiography or computed tomography (CT), only one patient (1.6%) had been diagnosed with NSF. However, the prevalence of NSF among the six patients in this cohort with stage 5 CKD who were receiving long-term haemodialysis was 17% [28]. Prince and colleagues retrospectively reviewed the charts of 83 121 patients who had received a GBCA between 1997 and 2007 at either of two academic medical centres in New York City [29]. Of these 83,121 patients, 15 (0.02%) were diagnosed with NSF. All 15 of these patients were among the 8997 patients who had received high-dose GBCA (>0.1 mmol kg⁻¹ body weight), yielding a prevalence of NSF of 0.17% among those exposed to high-dose GBCA. Among the 398 patients with stage 5 CKD who were included in this study, NSF was diagnosed in 11 (2.8%). However, this study was limited by its reliance upon passive reporting of NSF cases, rather than actively seeking cases by examining all individuals exposed to GBCAs for the presence or the absence of skin changes characteristic of NSF. Therefore, this and other retrospective studies likely underestimate the prevalence of NSF.

Although NSF predominantly affects patients with stage 5 CKD, cases have been reported in individuals with stage 4 [21,28] and stage 3 CKD [20]. NSF has also been reported in patients with acute kidney injury, who subsequently recovered normal renal function [30]. Thus, the occurrence of clinical features characteristic of NSF should trigger consideration of this diagnosis in any patient who has been exposed to a GBCA, regardless of the level of renal dysfunction.

What is the histopathology of skin biopsies in patients with NSF?

Skin biopsies of patients with NSF reveal a hypercellular dermis, few inflammatory cells and prominent dermal spindle cells [31]. Surface markers on these cells include CD34, CD45RO and type I procollagen, indicating that these cells are derived from circulating fibrocytes that have deposited in
<table>
<thead>
<tr>
<th>Study (location)</th>
<th>Year published</th>
<th>Type</th>
<th>GBCA exposure</th>
<th>NSF cases/ total patients</th>
<th>NSF cases/GBCA-exposed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marckmann et al. [18]</td>
<td>2006</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>N/A</td>
<td>13/370 (3.5%)</td>
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<td>Broome et al. [25]</td>
<td>2007</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>10/168 (6%)</td>
<td>N/A</td>
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<tr>
<td>Collidge et al. [26]</td>
<td>2007</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>14/1826 (0.8%)</td>
<td>13/421 (3.1%)</td>
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<td>Deo et al. [16]</td>
<td>2007</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>3/467 (0.6%)</td>
<td>3/87 (3.4%)</td>
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<td>Lauenstein et al. [78]</td>
<td>2007</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>N/A</td>
<td>8/312 (2.6%)</td>
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<tr>
<td>Othersen et al. [17]</td>
<td>2007</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>4/849 (0.5%)</td>
<td>4/261 (1.5%)</td>
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<td>Todd et al. [15]</td>
<td>2007</td>
<td>Cross-sectional and prospective</td>
<td>Gadopentetate dimeglumine</td>
<td>25/186 (13.4%)</td>
<td>16/54 (29.6%)</td>
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<tr>
<td>Prince et al. [29]</td>
<td>2008</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine, gadobenate dimeglumine, gadoteridol</td>
<td>N/A</td>
<td>11/398 (2.8%)</td>
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<td>Rydahl et al. [27]</td>
<td>2008</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>N/A</td>
<td>18/102 (17.6%)</td>
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<tr>
<td>Chen et al. [79]</td>
<td>2009</td>
<td>Retrospective</td>
<td>Gadodiamide</td>
<td>N/A</td>
<td>1/127 (0.8%)</td>
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<td>Chrysochou et al. [80]</td>
<td>2009</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine, gadofosveset trisodium</td>
<td>N/A</td>
<td>1/81 (1.2%)</td>
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<td>Heinz-Peer et al. [81]</td>
<td>2009</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine, gadoterate meglumine, gadobutrol, gadoteridol, gadobenate dimeglumine, gadoxetate disodium</td>
<td>6/552 (1.1%)</td>
<td>6/367 (1.6%)</td>
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<tr>
<td>Hope et al. [82]</td>
<td>2009</td>
<td>Retrospective</td>
<td>Gadopentetate dimeglumine</td>
<td>N/A</td>
<td>1/530 (0.2%)</td>
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<tr>
<td>Lee et al. [83]</td>
<td>2009</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine, gadobenate dimeglumine, gadoteridol, gadoxetate disodium</td>
<td>N/A</td>
<td>8/827 (1.0%)</td>
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<td>Janus et al. [84]</td>
<td>2010</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine, gadoterate meglumine, gadobenate dimenglumine</td>
<td>0/165 (0%)</td>
<td>N/A</td>
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<tr>
<td>Lemy et al. [85]</td>
<td>2010</td>
<td>Retrospective</td>
<td>Gadodiamide, gadoterate, meglumine</td>
<td>6/705 (0.9%)</td>
<td>5/33 (15.2%)</td>
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<tr>
<td>Martin et al. [86]</td>
<td>2010</td>
<td>Retrospective</td>
<td>Gadodiamide, gadobenate dimeglumine</td>
<td>N/A</td>
<td>8/1096 (0.7%)</td>
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<tr>
<td>Chow et al. [87]</td>
<td>2011</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine</td>
<td>N/A</td>
<td>1/97 (1.0%)</td>
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<tr>
<td>Kendrick-Jones et al. [88]</td>
<td>2011</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine, gadobutrol, gadobenate dimeglumine</td>
<td>N/A</td>
<td>5/522 (1.0%)</td>
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<tr>
<td>Alhadad et al. [89]</td>
<td>2012</td>
<td>Retrospective</td>
<td>Gadodiamide, gadopentetate dimeglumine, gadoterate meglumine, gadobenate dimeglumine, gadoxetate disodium, gadoteridol</td>
<td>N/A</td>
<td>0/129 (0%)</td>
</tr>
</tbody>
</table>

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*a This table includes results compiled from the listed studies only for patients with GFR < 15 mL/min. Broome et al. [13] calculated a disease prevalence per GBCA exposure but not per GBCA-exposed patient.
In the interstitium of the superficial dermis of patients with NSF, prominent elastic fibres interweave among the dermal collagen bundles and mucin deposits [3,5]. Multinucleated giant cells and dendritic cells that express CD68 and Factor XIIIa may also be present in the skin of patients with NSF [33]. Additional histological features that may be observed in skin biopsies of patients with NSF include osseous metaplasia, calcification and a mild, chronic inflammatory infiltrate. Given that the interlobular septae of subcutaneous adipose tissue may be affected in NSF, a deep-skin punch biopsy should be performed when this diagnosis is considered.

Gadolinium has been detected in affected skin by electron microscopy [34,35] as well as in skeletal muscle, lymph node, heart, lung, liver, adrenal gland, kidney, ileal wall, thyroid, eye, dura mater and cerebellum of patients with NSF [9,10,12,13]. Gadolinium has been quantified by mass spectrometry in affected skin [36], further supporting the causal role for gadolinium in the pathogenesis of NSF. It was not detected in skin biopsies obtained from patients who had normal renal function at the time of GBCA exposure [37].

What is gadolinium?

Gadolinium is a rare-earth metal of the lanthanide series with atomic number 64 in the periodic table of elements. Given its highly paramagnetic properties, gadolinium is used as a component of contrast agents administered during magnetic resonance (MR) imaging and angiography procedures. Because gadolinium is highly toxic in its free form, it is bound to an organic chelate when used as a contrast agent. The preparations of GBCAs that are administered during imaging procedures contain the gadolinium–chelate complex with variable amounts of excess chelate added to bind free gadolinium that is released from its chelate while stored in the bottle.

Commercially available GBCAs differ in the structure of their chelate (macrocyclic vs. linear) and in their charge (ionic vs. non-ionic). These properties determine the ease with which free gadolinium is released from the gadolinium–chelate complex. Whereas ionic and macrocyclic agents have the highest affinity for gadolinium, the risk of gadolinium dissociating from its chelate increases for non-ionic and linear agents [38]. Seven GBCAs have been approved by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA): gadobenate dimeglumine (MultiHance®),
gadobutrol (Gadavist®), gadodiamide (Omniscan®), gadopentetate dimeglumine (Magnevist®), gadoteridol (ProHance®), gadoversetamide (OptiMARK®) and gadoxetate disodium (Eovist® and Primovist®). In addition, gadofosveset trisodium (Ablavar® and Vasovist®) has been approved by the FDA for use in MR angiography and gadoterate meglumine (Dotarem®) has been approved by the EMA for use in both MR imaging and angiography (Fig. 4).

The major risk factors for developing NSF include the instability of the gadolinium–chelate complex, the cumulative dose of GBCA and the presence of renal dysfunction, either acute or chronic. Most cases of NSF have been reported in patients who received linear GBCAs, such as Omniscan® and Magnevist® [39]. This supports the hypothesis that the more easily free gadolinium can dissociate from the gadolinium–chelate complex, the more likely NSF is to develop. Thus, GBCAs with lower thermodynamic stability are more likely to predispose to the development of NSF. The risk of developing NSF also depends on the cumulative dose of GBCA, with higher cumulative doses leading to an increased risk of NSF [22]. However, some patients with CKD have developed NSF after receiving only a single infusion of GBCA [40]. Given that all GBCAs are eliminated by the kidneys, renal dysfunction increases the duration of time during which a patient is exposed to gadolinium after a GBCA-enhanced imaging procedure, thereby increasing that individual’s likelihood of developing NSF.

![Fig. 4. European Medicines Agency categorization of gadolinium-containing contrast agents by nephrogenic systemic fibrosis risk*](93–95). *Based on thermodynamic and kinetic properties. Reproduced with permission from Bernstein E.J., Kay J. Nephrogenic systemic fibrosis: A fibrosing disorder induced by gadolinium exposure. Int J Adv Rheumatol 2011;9(4):123–33.)
What is the pathophysiology of NSF?

Patients with normal renal function clear gadolinium–chelate complexes rapidly. However, in patients with impaired renal function, gadolinium–chelate complexes remain in the body longer. During this time, gadolinium may dissociate from its chelate and bind to tissue. Gadolinium deposition has been detected in biopsies of skin [34,35] and other tissues from NSF patients [9,12], but not in skin from individuals with normal renal function and without NSF [37]. Once gadolinium has dissociated from its chelate and is bound to tissue, circulating fibrocytes are attracted to these sites and release profibrotic cytokines, synthesise and secrete extracellular matrix and induce fibrosis [32]. Fibrocytes subsequently migrate to distant corporeal sites, promoting further fibrosis.

The current understanding of mechanisms of gadolinium-induced fibrosis is derived primarily from in vitro studies. Omniscan® induces the expression and production of several pro-inflammatory and profibrotic cytokines by human macrophages via signalling through Toll-like receptors (TLRs) 4 and 7 [41]. These cytokines include interleukin (IL)-4, IL-6, IL-13, interferon (IFN)-γ, vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGFβ), as well as the nuclear factor-κB (NFκB)-dependent cytokines CCL2, CCL8, CXCL10, CXCL11 and CXCL12 [41,42]. This cytokine induction is likely due to the gadolinium itself because the chelate alone, caldiamide, fails to induce expression of any of these cytokines. The relevance to NSF of the effect of gadolinium on macrophages is underscored by the localisation of gadolinium deposits to macrophages in skin biopsies from patients with NSF [43]. In addition, gadolinium induces macrophage apoptosis [44].

Human peripheral blood monocytes, which are precursors of macrophages, also produce the cytokines IL-4, IL-6, IL-13 and IFN-γ, and the growth factors VEGF and TGFβ after incubation with Omniscan® [45]. Incubation of monocytes with gadolinium chloride (GdCl3) yields similar cytokines and growth factors, indicating that this effect might be due to free, rather than chelated, gadolinium. Conditioned media from monocytes that had been exposed to either Omniscan® or GdCl3 can induce expression of α-smooth muscle actin (α-SMA) and expression and production of type 1 procollagen by dermal fibroblasts. Omniscan® and Magnevist® both activate dermal fibroblasts directly to increase expression of type I collagen [46]. The relevance of these effects to NSF is supported by the finding that many dermal fibroblasts from NSF patients are fully differentiated myofibroblasts that exhibit an activated fibrotic phenotype and produce increased amounts of types I and III collagen, fibronectin and hyaluronic acid. These fibroblasts maintain this phenotype after as many as 11 passages in culture, indicating persistent activation.

The tyrosine kinase inhibitor imatinib mesylate blocks signalling through the TGF-β and platelet-derived growth factor (PDGF) receptors, thereby decreasing extracellular matrix production [47]. Because treatment of NSF with imatinib mesylate decreases skin induration and dermal fibrosis, it is likely that binding of one or both of these profibrotic cytokines to their receptor is involved in the pathogenesis of NSF [48,49].

The contribution of renal dysfunction to the development of NSF has been studied using in vivo models of NSF. NSF-like skin lesions have been induced in Hannover Wistar rats with normal renal function after five times weekly intravenous injections of Omniscan® for 4 weeks. In these animals, gadolinium deposition was detected in affected skin, bone and liver [50]. In another study, renally impaired Hannover Wistar rats that had undergone 5/6 nephrectomy developed similar skin lesions, starting 5 days after the last of five daily intravenous doses of Omniscan® [51]. Tissue gadolinium levels were also elevated in skin biopsies from these animals. Similar to humans, not all rats treated intravenously with GBCA developed skin lesions. Further studies are needed to explore factors other than GBCA exposure that may contribute to the development of NSF.

In summary, in vitro studies have shown that macrophages and monocytes exposed to GBCA produce pro-inflammatory and profibrotic cytokines that subsequently activate dermal fibroblasts. TLRs and NFκB pathways may play important roles in this process. In addition, GBCA may also activate fibroblasts directly. Once activated, fibroblasts maintain a profibrotic phenotype and produce increased amounts of extracellular matrix components. Clinically, this manifests as dermal and visceral fibrosis.

The question of what factors cause gadolinium to deposit in the tissues of some patients and subsequently to drive fibrosis remains to be answered. Renal failure is the most important risk factor for NSF because it prolongs the half-life of GBCA in the circulation: for Omniscan®, the half-life increases...
from 1 to 2 h in healthy individuals with normal renal function to about 30 h in patients with stage 5 CKD [52]. Other potential risk factors might affect the stability and transmetallation of gadolinium–chelate complexes or might prime cells to be more susceptible to gadolinium, either free or bound to chelate. Treatment with erythropoietin and with intravenous iron has each been proposed to exacerbate NSF [53]. However, the specific mechanism by which either of these drugs might modulate fibrosis and the relative importance of other potential risk factors remain to be elucidated.

**How is NSF treated?**

Many therapies have been tried in patients with NSF (Table 4). Unfortunately, most have failed to induce significant and lasting improvement. Treatments that have been found to be ineffective in patients with NSF include oral and topical corticosteroids, histamine-2 (H2) receptor antagonists, thalidomide and cyclosporine [54]. Plasmapheresis [55–57], extracorporeal photopheresis [58–62], ultraviolet-A phototherapy [62–66], sirolimus [57,67], sodium thiosulphate [68–70] and renal transplantation [71–74] have been variably effective in treating NSF. Treatment with imatinib mesylate has improved cutaneous changes and joint mobility in patients with NSF [48,49].

**Where do we go from here?**

Although the implementation of restrictive guidelines for GBCA administration has decreased the number of new cases of NSF [75], this change in practice has not eradicated the disease. As long as GBCAs continue to be used as the contrast agent of choice for MR imaging procedures, there will be new cases of NSF. Rheumatologists are in a key position to identify and diagnose patients with this disease. We must enquire about and look for skin changes when evaluating a patient with CKD, who has undergone an imaging study in which he or she may have received a GBCA. Most of all, we need to be judicious in our use of GBCAs. For every MR imaging study that we order, we should reflect upon whether a GBCA is really needed or whether the same information can be obtained without the use of this contrast agent. When we see patients in the hospital in our role as consultants, we must remind the health-care professionals caring for them about limiting the use of GBCAs. We must educate our medical students, residents and fellows about the potential danger of GBCAs and the debilitating nature of NSF.

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**References**


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**Table 4**

<table>
<thead>
<tr>
<th>Therapies Attempted for NSF.</th>
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<th>Promising effectiveness</th>
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</thead>
<tbody>
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