REVIEW

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Nephrogenic systemic fibrosis and its association with gadolinium exposure during MRI

ABSTRACT

Nephrogenic systemic fibrosis (NSF) is a newly recognized systemic disorder characterized by widespread tissue fibrosis in patients with impaired renal function. Recent reports suggest that NSF is associated with exposure to gadolinium-based contrast agents used in magnetic resonance imaging. NSF can be very debilitating and can lead to serious complications and death. Health care providers should exercise caution when considering the use of gadolinium-based imaging studies in patients with renal dysfunction.

KEY POINTS

NSF seems to arise in roughly 3% of patients with renal insufficiency who receive gadolinium, although the data are somewhat sketchy and the true incidence might be higher if the NSF is specifically looked for.

Manufacturers of all available gadolinium contrast agents now must include a boxed warning about the risk of NSF in patients with acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/minute/1.73 m^2) and in patients with acute renal insufficiency of any severity due to hepatorenal syndrome or in the perioperative liver transplantation period.

As yet, we have no effective treatment for NSF. If the patient is already on hemodialysis, it may be reasonable to perform hemodialysis immediately after exposure to gadolinium and again the next day.

THE USE OF GADOLINIUM as a contrast agent in magnetic resonance imaging (MRI) in patients with impaired kidney function has come under scrutiny because of recent reports of a potential association between its use and nephrogenic systemic fibrosis (NSF).

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This entity was first identified in the United States in 1997. Cowper et al[1] in 2000 described 15 hemodialysis patients who developed thickening and hardening of the skin with brawny hyperpigmentation, papules, and subcutaneous nodules on the extremities.

This "new disease" was initially called "nephrogenic fibrosing dermopathy," as it was exclusively seen in patients with renal impairment and was thought to affect only the skin and subcutaneous tissue. With growing evidence of the extent and pathogenicity of the fibrosis in visceral organs, the nomenclature was changed to NSF, to better reflect the systemic nature of the disease.

PRESENTATION: MILD TO DEVASTATING

NSF has thus far been reported only in patients with renal impairment, most of whom were dialysis-dependent. It does not seem to be more common in one sex or the other, in any age range, or in any ethnic group. It can range in severity from mild to a devastating scleroderma-like systemic fibrosing disorder.

Cutaneous changes are the most predom-

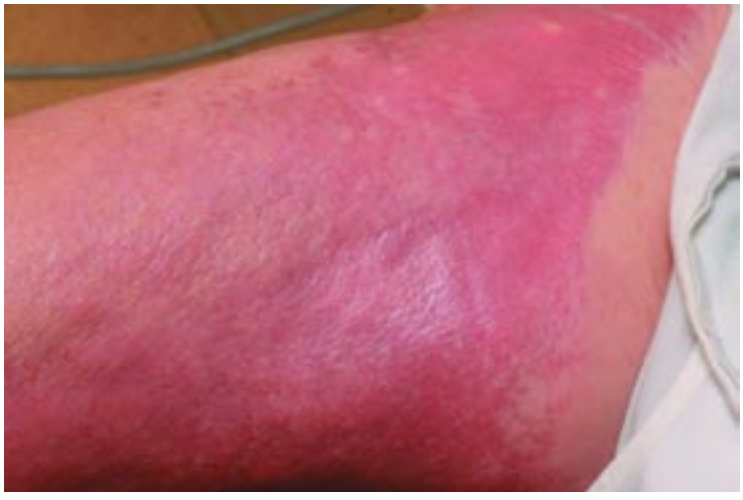

FIGURE 1. Typical skin lesions of nephrogenic systemic fibrosis (indurated erythematous plaques) affecting the lower extremities.

NSF causes dermal hardening and tethering and textured plaques, papules, or nodules

inant and impressive manifestations. NSF typically causes dermal hardening with tethering to deep dermal tissues, giving the skin the appearance of textured plaques, papules, or nodules with irregular edges and a brawny wooden texture to palpation (FIGURE 1). The lesions can be erythematous or brown-pigmented and can be painful and pruritic. NSF typically presents between the ankles and the thighs in a symmetric fashion and progresses proximally and distally to involve the entire lower extremities. Upper extremity involvement occurs frequently, but usually with lower extremity disease.[2] The trunk is involved less commonly than the legs and arms, and usually late in extensive disease. The face is typically spared (FIGURE 2).

NSF can cause loss of motion and contractures in multiple joints, leading to almost total loss of function and devastating debility within a short time—days to a few weeks.[2] These contractures are attributed to periarticular fibrosis of the overlying skin and subcutaneous tissue rather than to erosive joint disease. About 5% of patients develop a fulminant form of NSF[3]; these patients may become wheelchair-dependent.

The heart, lungs, skeletal muscle, and diaphragm can also be involved, sometimes leading to serious complications and death.[4–6]

The disease is usually progressive and unremitting. Mendoza et al,[7] in a review of 12 cases of NSF, reported that the disease had a progressive course in 6 patients, of whom 3 died within 2 years and 3 were ultimately confined to a wheelchair. More severe findings and rapid progression of the skin disease are associated with a poor prognosis.

Todd et al[8] prospectively examined 186 dialysis patients to look for possible NSF. Of those with skin changes consistent with NSF, 48% died within 2 years, compared with 20% of those without these skin changes. Cardiovascular causes accounted for 58% of the deaths in patients with cutaneous changes of NSF and for 48% of the deaths in patients without these changes. Most of the excess deaths occurred within 6 months after the skin examination, suggesting an increased risk for early death in patients with skin changes suggestive of NSF.

DIAGNOSIS OF NSF IS CLINICAL

At presentation, NSF is frequently misdiagnosed and treated as cellulitis or edema. However, now that subspecialists—especially dermatologists, rheumatologists, and nephrologists—are becoming more aware of it, the correct diagnosis is being made earlier.

NSF should be suspected in any patient with underlying renal dysfunction—especially if on dialysis and if he or she has received a gadolinium contrast agent during MRI—who develops scleroderma-like cutaneous lesions affecting the distal extremities. Because most health care providers are still unfamiliar with this emerging disease, patients with renal impairment and suspected NSF should be referred to a rheumatologist or dermatologist to confirm the diagnosis, which is mainly entertained on a clinical basis. There is no laboratory biomarker for NSF.

A deep incisional skin biopsy may aid in the diagnosis. Due to the regional distribution of the disease, sampling error may occur, and repeat biopsy is warranted if the initial biopsy is nondiagnostic but the clinical picture suggests NSF.

Histopathologic examination typically shows lesions containing proliferation of dermal spindle cells, thick collagen bundles with surrounding clefts, and a variable amount of mucin and elastic fibers.[2] A characteristic and almost pathognomonic staining profile is the

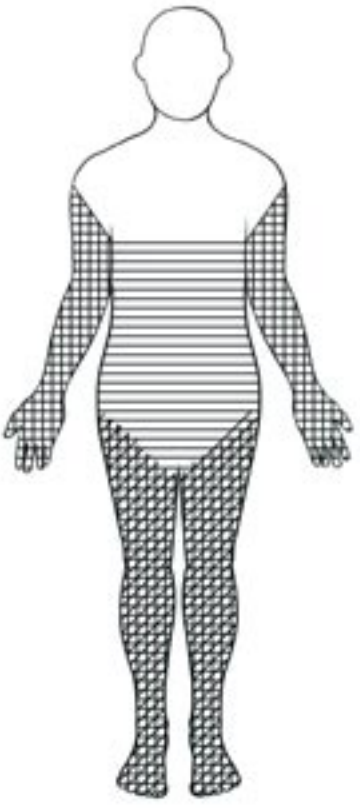

FIGURE 2. The pattern of involvement is usually symmetric. The lesions most often affect the lower extremities, followed by the upper and lower extremities and then the trunk and upper and lower extemities. The face is usually spared.

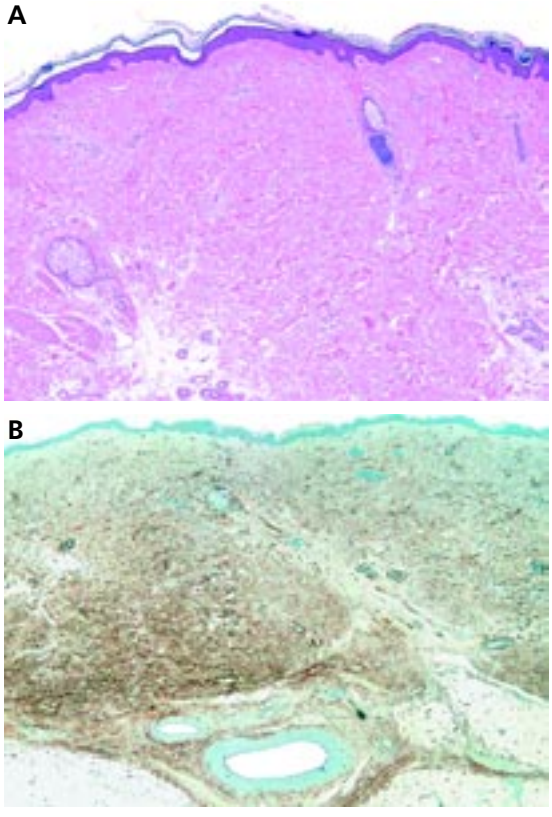

FIGURE 3. Biopsy specimen from the skin of a lower extremity of a patient with nephrogenic systemic fibrosis (NSF) (hematoxylin and eosin stain) shows increased spindled fibrocytes and collagen bundles typical of NSF (A) and CD34-positive immunohistochemical staining in fibroblast-like cells (B) characteristic of NSF.

immunohistochemical identification of CD34 reactivity in the fibroblast-like cells (FIGURE 3). Cells expressing CD34 are normally found in the umbilical cord, the bone marrow (as pluripotential hematopoietic stem cells), and in the vascular endothelium. How they come to be in the skin is still speculative, but their presence suggests that circulating fibrocytes migrate from the bone marrow and deposit in the skin and other organs.[9,10]

Pulmonary function testing can be done to rule out lung involvement and transthoracic two-dimensional echocardiography can be done to rule out possible cardiomyopathy if these conditions are suggested by examination at the time of diagnosis.[7] Muscle biopsy is not necessary to determine the extent of systemic involvement, since the findings do not necessarily correlate with other systemic involvement.

NSF in the early stages is often misdiagnosed as cellulitis or edema

DIFFERENTIAL DIAGNOSIS

Other disorders that can cause thickening and hardening of the skin of the extremities and trunk include systemic sclerosis or scleroderma, scleromyxedema, and eosinophilic fasciitis (TABLE 1). However, skin thickening, tethering, and hyperpigmentation in a patient with chronic kidney disease or end-stage renal disease after exposure to gadolinium-containing contrast agents suggests NSF.

An important diagnostic feature of NSF is that it spares the face, a finding derived from all reported and confirmed cases of NSF (FIGURE 2). In contrast, scleromyxedema, systemic scleroderma, and morphea often involve the face.

TABLE 1

Differential diagnosis of nephrogenic systemic fibrosis

CONDITION	DISTINGUISHING FEATURES
Nephrogenic systemic fibrosis	Renal insufficiency (acute or advanced chronic, on renal replacement therapy or not) Primarily involves the lower and upper extremities (in symmetric fashion) and spares the face Gadolinium exposure
Scleromyxedema	Paraproteinemia Often involves the face
Systemic scleroderma/morphea	CREST features (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) may be present Often involves the face Anticentromere or anti-SCL70 antibodies may be detected
Eosinophilic fasciitis	Eosinophils on skin biopsy including muscle fascia
Fibrosis due to drugs, silica, or organic solvents	History of exposure to respective toxins
Amyloidosis	Congo red staining on histologic examination of affected organs (kidneys, anterior abdominal adipose tissue, rectum)
Calciphylaxis	Renal insufficiency (chronic kidney disease and, mainly, end-stage renal disease on renal replacement therapy) Areas of central necrosis at advanced stages Often associated with increased calcium-phosphorus product and severe hyperparathyroidism
Eosinophilia-myalgia syndrome	Ingestion of L-tryptophan supplements
Pretibial myxedema	Hypothyroidism
Porphyria cutanea tarda	Involvement of sun-exposed skin areas Genetic testing
Graft-vs-host disease	Transplant recipient: especially allogeneic bone marrow transplantation

An important diagnostic feature of NSF is that it spares the face

Scleromyxedema is often associated with monoclonal gammopathy (usually an immunoglobulin G lambda paraproteinemia) whereas NSF is not.

Scleroderma is supported by the findings of Raynaud's phenomenon, antinuclear antibodies, and either anticentromere or anti-DNA topoisomerase I (Scl-70) antibodies, but the absence of these antibodies does not necessarily rule it out.

Eosinophilic fasciitis is diagnosed on the basis of histologic examination of a deep wedge skin biopsy specimen that includes fascia.

Other diagnoses that should be considered include amyloidosis and calciphylaxis.

ASSOCIATION WITH GADOLINIUM: WHAT IS THE EVIDENCE?

Case series

The association of gadolinium use with NSF has been described in several case reports and case series.

Grobner[11] reported that administration of gadodiamide (Omniscan, a gadolinium compound) for MRI was associated with NSF in five patients on chronic hemodialysis who had end-stage renal disease. Their ages ranged from 43 to 74 years, and they had been on dialysis from 10 to 58 months. The time of onset of NSF ranged from 2 to 4 weeks after exposure to gadodiamide.

Marckmann et al[12] reported that NSF developed in 13 (3.5%) of 370 patients with severe kidney disease who received gadodiamide. Five of the 13 patients had stage 5 (advanced) chronic kidney disease and were not yet on renal replacement therapy, 7 were on hemodialysis, and 1 was on peritoneal dialysis. The time of onset ranged from 2 to 75 days (median 25 days) after exposure.

Kuo et al[13] similarly estimated the incidence of NSF at approximately 3% in patients with severe renal failure who receive intravenous gadolinium-based contrast material for MRI.

Broome et al[14] reported that 12 patients developed NSF within 2 to 11 weeks after receiving gadodiamide. Eight of the 12 patients had end-stage renal disease and were on hemodialysis; the other 4 patients had acute kidney injury attributed to hepatorenal syndrome, and 3 of these 4 patients were on hemodialysis.

Khurana et al[15] reported that 6 patients on hemodialysis developed NSF from 2 weeks to 2 months after receiving a dose of gadodiamide of between 0.11 and 0.36 mmol/kg. These doses are high, and the findings suggest an association between the gadolinium dose and NSF. The dose approved by the US Food and Drug Administration (FDA) is only 0.1 mmol/kg, and the use of gadolinium is approved only in MRI. However, higher doses (0.3–0.4 mmol/kg) are widely used in practice for better imaging quality in magnetic resonance angiography (MRA).

The true incidence of NSF is difficult to determine

Deo et al[16] reported 3 cases of NSF in 87 patients with end-stage renal disease who underwent 123 radiologic studies with gadolinium. No patient with end-stage renal disease who was not exposed to gadolinium developed NSF, and the association between exposure to gadolinium and the subsequent development of NSF was statistically significant ($P = .006$). The authors concluded that each gadolinium study presented a 2.4% risk of NSF in end-stage renal disease patients.

This retrospective study is flawed by not having been cross-sectional or case-controlled, since the other 84 patients who received gadolinium were not examined at all to establish the absence of NSF.

Case-control studies

More evidence of association of NSF with gadolinium exposure comes from other reports.

Physicians in St. Louis, MO,[17] identified 33 cases of NSF and performed a case-control study, matching each of 19 of the patients (for whom data were available and who met their entry criteria) with 3 controls. They found that exposure to gadolinium was independently associated with the development of NSF.

Sadowski et al[18] reported that 13 patients with biopsy-confirmed NSF all had been exposed to gadodiamide and one had been exposed to gadobenate (MultiHANCE) in addition to gadodiamide. All 13 patients had renal insufficiency, with an estimated glomerular filtration rate (GFR) less than 60 mL/minute/1.73 m^2. The investigators compared this group with a control group of patients with renal insufficiency who did not develop NSF. The NSF group had more proinflammatory events ($P < .001$) and more gadolinium-contrast-enhanced MRI examinations per patient ($P = .002$) than the control group.

Marckmann et al[19] compared 19 patients who had histologically proven cases of NSF and 19 sex- and age-matched controls; all 38 patients had chronic kidney disease and had been exposed to gadolinium. Patients with NSF had received higher cumulative doses of gadodiamide and higher doses of erythropoietin and had higher serum concentrations of ionized calcium and phosphate than did their controls, as did patients with severe NSF compared with those with nonsevere NSF .

Comment. All the above reports are limited by their study design and suffer from recognition bias because not all of the patients with severe renal insufficiency who were exposed to gadolinium were examined for possible asymptomatic skin changes that might be characteristic of NSF. Therefore, it is impossible to be certain that all of the patients classified as not having NSF truly did not have it or did not subsequently develop it. Furthermore, the reports lacked standardized diagnostic criteria. Hence, the real prevalence and incidence of NSF are difficult to determine.

A cross-sectional study

As mentioned above, Todd et al[8] examined

TABLE 2

Approved gadolinium contrast agents for magnetic resonance imaging

GADOLINIUM FORMULATION	CHARGE	STRUCTURE
Gadodiamide (Omniscan)	Nonionic	Linear
Gadopentetate (Magnevist)	Ionic	Linear
Gadoversetamide (OptiMARK)	Nonionic	Linear
Gadoteridol (ProHance)	Nonionic	Cyclic
Gadobenate (MultiHance)	Ionic	Linear

186 dialysis patients for cutaneous changes of NSF (using a scoring system based on hyperpigmentation, hardening, and tethering of skin on the extremities). Patients who had been exposed to gadolinium had a higher risk of developing these skin changes than did nonexposed patients (odds ratio 14.7, 95% confidence interval 1.9–117.0). More importantly, the investigators found cutaneous changes of NSF in 25 (13%) of the 186 patients, 4 of whom had prior skin biopsies available for review, each revealing the histologic changes of NSF. This study suggests that NSF may be more prevalent than previously thought.

Ionic gadolinium is highly toxic and is therefore bound to a chelate for use in vivo

Is kidney dysfunction always present?

All the reported patients with NSF had underlying renal impairment. The renal dysfunction ranged from acute kidney injury to advanced chronic kidney disease (estimated GFR < 30 mL/minute/1.73 m^2) and end-stage renal disease on renal replacement therapy, ie, hemodialysis or peritoneal dialysis. The incidence of NSF does not seem to be related to the cause of the underlying kidney disease.

What other diseases or comorbidities can be associated with NSF?

It is still unclear why not every patient with advanced renal failure develops NSF after exposure to gadolinium.

A variety of complex diseases and conditions have been reported to be associated with NSF, with no clear-cut evidence of causality or trigger. These include hypercoagulability states, thrombotic events, surgical procedures (especially those with reconstructive vascular components), calciphylaxis, kidney transplantation, hepatic disease (hepatorenal syndrome, liver transplantation, and hepatitis B and C), idiopathic pulmonary fibrosis, systemic lupus erythematosus, hypothyroidism, elevated serum ionized calcium or serum phosphate, hyperparathyroidism, and metabolic acidosis. A possible explanation is that most of these conditions are associated with an increased use of MRI or MRA testing (eg, in the workup for kidney or liver transplantation).

Many drugs have also been reported to be associated with NSF, including high-dose erythropoietin,[20] sevelamer (Renagel),[21] and, conversely, lack of angiotensin-converting enzyme inhibitor therapy,[22] but none of these findings has been reproduced to date.

GADOLINIUM CHARACTERISTICS AND PHARMACOKINETICS

Gadolinium is a rare-earth lanthanide metallic element (atomic number 64) that is used in MRI and MRA because of its paramagnetic properties that enhance the quality of imaging. Its ionic form (Gd^{3+}) is highly toxic if injected intravenously, so it is typically bound to a "chelate" to decrease its toxicity.[23] The chelate stabilizes Gd^{3+} and thereby prevents its dissociation in vivo. These Gd-chelates can be classified (TABLE 2) according to their charge (ionic vs nonionic) and their structure (linear vs cyclic).

Most of the reported cases of NSF have been in patients who received gadodiamide, a nonionic, linear agent. Why gadodiamide has the highest rates of association with NSF is still unclear; perhaps it is simply the most widely used agent. Also, linear Gd compounds may be less stable and more likely to dissociate in vivo. The updated FDA Public Health Advisory in May 2007 warned against the use of all gadolinium-containing contrast agents for MRI, not just gadodiamide.

After intravenous injection, Gd-chelate equilibrates rapidly (within 2 hours) in the extracellular space. Very little of it enters into cells or binds to proteins. It is eliminated unchanged in the glomerular filtrate with no tubular secretion. In a study by Joffe et al,[24] the elimination half-life of gadodiamide in patients with severely reduced renal function was considerably longer than in healthy volunteers (34.3 hours ± 22.9 vs 1.3 hours ± 0.25).

Since gadolinium compounds are not protein-bound and have a limited volume of distribution, they are typically removed by hemodialysis. Joffe et al found that an average of 65% of the gadodiamide was removed in a single hemodialysis session. However, they did not describe the specific features of the hemodialysis session, and it took four hemodialysis treatments to remove 99% of a single dose of gadolinium.[24] A dialysis membrane with high permeability (large pores) seems to increase the clearance of the Gd-chelate during hemodialysis.[25]

Peritoneal dialysis may not remove gadolinium as effectively: Joffe et al[24] reported that after 22 days of continuous ambulatory peritoneal dialysis, only 69% of the total amount of gadodiamide had been excreted, suggesting a very low peritoneal clearance.

SPECULATIVE PATHOGENESIS

Although a causal relationship between gadolinium use in patients with renal dysfunction and NSF has not been definitively established, the data derived from case reports assuredly raise this suspicion. Furthermore, on biopsy, gadolinium can be found in the skin of patients with NSF, adding evidence of causality.[26–28]

Physical therapy and pain control may have benefits in NSF

The mechanism by which Gd^{3+} might trigger NSF is still not understood. A plausible speculation is that if renal function is reduced, the half-life of the Gd-chelate molecule is significantly increased, as is the chance of Gd^{3+} dissociating from its chelate, leading to increased tissue exposure. Vascular trauma and endothelial dysfunction may allow free Gd^{3+} to enter tissues more easily, where macrophages phagocytose the metal, produce local profibrotic cytokines, and send out signals that recruit circulating fibrocytes to the tissues. Once in tissues, circulating fibrocytes induce a fibrosing process that is indistinguishable from normal scar formation.[29]

TREATMENTS LACK DATA

There is no consistently successful treatment for NSF.

In isolated reports, successful kidney transplantation slowed the skin fibrosis, but these findings need to be confirmed.[30,31] Data from case reports should be interpreted very cautiously, as they are by nature sporadic and anecdotal. Moreover most of the reports of NSF were published on Web sites or as editorials and did not undergo exhaustive peer review. Because the evidence is weak, kidney transplantation should not be recommended as a treatment for NSF.

Oral steroids, plasmapheresis, extracorporeal photopheresis, thalidomide, topical ultraviolet-A therapy, and other treatments have yielded very conflicting results, with only anecdotal improvement of symptoms. In a recent case report,[32] the use of intravenous sodium thiosulfate in addition to aggressive physical therapy provided some benefit by reducing the pain and improving the skin lesions.

Because of the lack of strong evidence of efficacy, we cannot advocate the use of any of these treatments until larger clinical trial results are available. Aggressive physical therapy along with appropriate pain control may have benefits and should be offered to all patients suffering from NSF.

Avoid gadolinium exposure in patients with renal insufficiency

The FDA[33] recently asked manufacturers to include a new boxed warning on the product labeling of all gadolinium-based contrast agents (Magnevist, MultiHance, Omniscan, OptiMARK, ProHance), due to risk of NSF in patients with acute or chronic severe renal insufficiency (GFR < 30 mL/minute/1.73 m^2) and in patients with acute renal insufficiency of any severity due to hepatorenal syndrome or in the perioperative liver transplantation period.

For the time being, gadolinium should be contraindicated in patients with acute kidney injury and chronic kidney disease stages 4 and 5 and in those who are on renal replacement therapy (either hemodialysis or peritoneal dialysis). If an MRI study with gadolinium-based contrast is absolutely required in a patient with end-stage renal disease or advanced chronic kidney disease, an agent other than gadodiamide should be used in the lowest possible dose.

Will hemodialysis prevent NSF?

In a patient who is already on hemodialysis, it seems prudent to perform hemodialysis soon after gadolinium exposure and again the day after exposure to increase gadolinium elimina-

tion. However, to date, there are no data to support the theory that doing this will prevent NSF.

Because peritoneal dialysis has been reported to clear gadolinium poorly, use of gadolinium is contraindicated. If gadolinium is absolutely needed, either more-aggressive peritoneal dialysis (keeping the abdomen "wet") or temporary hemodialysis may be considered.

For patients with advanced chronic kidney disease who are not yet on renal replacement therapy, the use of gadolinium is contraindicated, and hemodialysis should not be empirically recommended after gadolinium exposure because we have no evidence to support its utility and because hemodialysis may cause harm.

Nephrology consultation should be considered before any gadolinium use in a patient with impaired renal function, whether acute or chronic. Cleveland Clinic guidelines regarding the use of gadolinium-based contrast agents in patients with renal dysfunction are available at **www.ccjm.org/ccjm_pdfs_toc/Feb08_Issa_NSF_Policy.pdf**.

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