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REVIEW

Nephrogenic systemic fibrosis and the use of gadolinium-based contrast agents

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Abstract Nephrogenic systemic fibrosis (NSF) is a disease seen exclusively in patients with decreased renal function. The use of gadolinium-based contrast agents (GBCAs) has a strong association with NSF. Linear non-ionic GBCAs that are more prone to release free gadolinium are the more likely to cause NSF. The number of reported cases has increased recently, and there are currently nine pediatric cases, the patients ranging in age from 8 years to 19 years, and the oldest adult patient is 87 years of age. The most successful treatment is improvement of renal function with renal transplantation or with recovery of acute kidney injury. NSF can be severely debilitating and even fatal. Avoidance of a GBCA in patients at risk, or limitation of the dose in the patients who need gadolinium enhancement, is recommended.

Keywords Nephrogenic systemic fibrosis · Magnetic resonance imaging · Kidney disease · Gadolinium · Contrast agents · End-stage renal disease

Introduction

Nephrogenic systemic fibrosis (NSF) was first seen in 1997, and the first published description by Cowper et al. did not appear until 2000 [1]. The original name for this disorder was nephrogenic fibrosing dermopathy, based on the predominant skin findings. As more severe cases emerged and autopsy cases were reviewed, it became evident that this was a systemic disease, and the name was changed to nephrogenic systemic fibrosis (NSF) in 2005 [2]. It is seen exclusively in patients with decreased renal function (acute or chronic), and the majority of these patients were on dialysis when they developed the disease.

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Clinical findings

NSF is seen in all age ranges, with the youngest patient developing NSF at 8 years of age [3–5] and the oldest at 87 years of age, with no gender or race predilection [6]. The primary manifestations of NSF are the skin findings. The skin is raised and thickened with edema. Erythema of the area frequently causes NSF to be misdiagnosed as resistant cellulitis. Areas of skin can also by hyperpigmented. The most frequent areas of involvement are the lower extremity, followed by the upper extremity and trunk. The skin of the head and neck are spared, which helps one to differentiate it from scleromyxedema, which typically involves the head and neck [7]. Though the skin is spared in the head and neck, extra-cutaneous manifestation on the head can include a yellow plaque of the sclera [8].

Biopsy of a skin lesion will show fibrosis of the dermis that extends down into the subcutaneous adipose, fascia and muscle. A deep biopsy is recommended to see this deep extension [6]. There are heavy mucin deposits, with much collagen deposition with clefts between the collagen. There are many spindle-shaped cells that have been identified as fibrocytes by the presence of CD34 and procollagen [9], though, in clinical practice, staining for these entities is not necessary to make the diagnosis [5]. Markers of fibrosis such as transforming growth factor beta 1 and trans-glutaminase are up-regulated in biopsy samples [10, 11].

Even with the erythema, fibrosis and presence of many fibrocytes, there are typically no inflammatory cells or rarely only a scant lymphocytic infiltrate [12].

Disabling and painful joint contractures are prominent in NSF. The joints themselves are not affected, but it is fibrosis of the skin, fascia and muscle that causes the contractures [13]. Nerve conduction studies demonstrate that peripheral nerve involvement also contributes to the weakness [14]. A review of the literature showed a 28% mortality rate for reported cases [7]. Many of those deaths were related to the cessation of dialysis because of the morbidity from the pain and immobility and included a 15-year-old boy who had had NSF for 4 years [15]. However, there was one case in which progressive fibrosis of the diaphragm directly resulted in death of the patient from respiratory failure because of the inability to ventilate [16]. Details of pediatric cases of NSF are listed in Table 1, and systemic tissue involvement is listed in Table 2.

Diagnosis

There is no standard criterion for the diagnosis of NSF. Todd et al. used physical examination alone to evaluate for hyperpigmentation, hardening, and tethering of the skin as criteria for diagnosis of NSF in a series of 17 dialysis patients. However, all other published series have required a skin biopsy to confirm the diagnosis. The presence of renal dysfunction, together with the above physical examination findings, and skin biopsy findings have been suggested as adequate criteria for diagnosis [6]. A history of the patient's receiving a gadolinium (Gd)-containing contrast agent (GBCA) is helpful but not required, since there are at least eight case reports of patients with NSF who had not received Gd prior to the diagnosis [14, 17–22].

Differential

Several skin diseases should be considered in the differential diagnosis. Scleromyxedema-like cutaneous disease was the original name given to NSF, because of the similar skin findings and biopsy findings. Scleromyxedema could not be differentiated from NSF when only the biopsies were reviewed, even though immunohistochemical staining for CD34, factor XIIIa, CD31, smooth muscle actin, CD68, colloidal iron, and procollagen-I was used. Differentiation requires clinical correlation. Scleromyxedema skin changes typically involve the head and neck, though NSF skin changes spare the head and neck. Scleromyxedema is also associated with a monoclonal paraprotein, and NSF has no serological marker [23]. Scleroderma involves thickening of the skin of the extremities and is easily differentiated by the presence of SCL-70.

Spanish toxic oil syndrome and eosinophilic myalgia are not clinically significant differential diagnoses because they are rare disorders. However, they are typically included in the differential diagnosis because they, too, are fibrosing skin disorders that are induced by a toxic substance [24, 25]. Amyloid and calciphylaxis are clinically significant diagnoses to differentiate because of the increased prevalence in dialysis patients. Calciphylaxis can start out as skin nodules, but this typically progresses to ulcerated skin lesions, and NSF does not develop into ulcerations. Amyloid can be easily differentiated by the presence of Congo red staining on biopsy.

Association with gadolinium

The etiology of NSF was a mystery until Grobner reported that five of nine dialysis patients from Austria who had received gadodiamide developed NSF, in an early online release article in January 2006 [26]. This was followed by a report from the Danish Medicines Agency in May 2006, reporting these five Austrian patients and 20 more Danish dialysis patients that developed NSF after receiving gadodiamide [27]. Based on these two reports, the United States Food and Drug Administration (FDA) issued its first warning about the association of NSF with Gd-based contrast agents in June of 2006.

After these initial reports there have been series of reports documenting the association of NSF with GBCAs [28]. The relative risk of developing NSF after exposure to a GBCA vs no exposure is reported as 6.67, 8.97, 22.3 and 32.5 in four studies [17, 29–31]. As in most published case reports, the GBCA used in those studies was gadodiamide, except in the report by Deo et al. in which two patients with NSF had received gadodiamide and one patient had received gadopentetate dimeglumine [30]. The prevalence of NSF after a dose of GBCA is estimated to be 2.4% in one study [30] and 1.5% in another [31]. A double dose of a GBCA increases the relative risk of developing NSF to 12.1 compared with that of a single dose [29], and multiple doses vs a single dose increases the relative risk from 6.67 to 44.5 [31]. There are several case reports of NSF developing in patients with chronic kidney disease (CKD) stage 4 and 5, but, in a study of a large population of patients who received gadodiamide, the incidence was zero for 592 patients, making the incidence less than 0.2% [31]. In a veterans affairs hospital where gadoteridol (the only cyclic GBCA approved in the USA) is the only GBCA used, the incidence of NSF was zero in 141 chronic dialysis patients exposed to 198 doses [32]. Other agents have not been studied.

Table 1 Pediatric cases of nephrogenic systemic fibrosis (NSF). Age given is in years at the time of diagnosis. *ESRD* end-stage renal disease, *CKD* chronic kidney disease, *Cr* creatinine, *MRA* magnetic resonance angiography, *MRI* magnetic resonance imaging, *NFD* nephrogenic fibrosing dermopathy

Author	Year of publication	Age	Gender	Kidney disease	Cause of renal failure	Treatment	GBCA	Number of studies with a GBCA	Outcome
Jain et al. [4, 67]	2004	19	Male	Failed transplant on hemodialysis	Multicystic dysplastic kidney disease	Prednisone for 5 months	Gadodiamide	13 MRAs, 9 prior to diagnosis of NSF	Mild improvement of the plaques
		9	Male	ESRD on peritoneal dialysis	Focal sclerosing glomerulonephritis	Renal transplantation	Gadodiamide	Single MRA	Died from presumed pulmonary embolus 3 days after receiving his transplant
Jan et al. [5]	2003	16	Female	Failed transplant on hemodialysis	Brachio-otorenal syndrome	Renal transplantation	Not mentioned	Not mentioned	Improvement in induration of skin
		8	Male	ESRD on peritoneal dialysis	Membranoproliferative glomerulonephritis type II	Renal transplantation	Not mentioned	Not mentioned	Improvement of skin lesions
Auron et al. [3]	2006	8	Male	ESRD on peritoneal dialysis	Membranoproliferative glomerulonephritis type II	Two renal transplantations	Not mentioned	Not mentioned	Muscle atrophy, wheelchair bound and dependent on narcotics for pain control
		19 [a]	Male	CKD stage IV	Nephrotoxicity from cedofovir	Extracorporeal photophoresis	Not mentioned	Not mentioned	Partial resolution
DiCarlo et al. [68]	2007	17	Male	Failed transplant on peritoneal dialysis	Not mentioned	Topical steroid administration, compression stockings, intravenous treatment with methylprednisolone and weekly administration of methotrexate	Not mentioned	Not mentioned	Near complete resolution of active cutaneous NFD lesions
Krous et al. [15]	2007	11	Male	CKD stage V	Bilateral renal diffuse large cell lymphoma	Renal transplantation	Not mentioned	13 MRIs	Died when dialysis was discontinued 4 days after a cardiac arrest during his transplant operation
Sanchez-Ross et al. [69]	2007	14	Female	Acute kidney injury requiring temporary dialysis. Cr returned to normal	Diffuse proliferative lupus nephritis and acute tubular necrosis	Hydroxychloroquine	Not mentioned	Not mentioned	Decrease in induration and discomfort after 6 months

[a] Symptoms began when the patient was aged 15 years

Table 2 Extra-cutaneous tissue involvement seen in autopsy cases [15, 16, 70, 71]

NSF systemic involvement	
Myocardium	Muscle
Pericardium	Bone
Lungs	Dura mater
Pleura	Kidney
Diaphragm	Testes

Gd in tissue

Gd in patients with normal renal function can deposit in bone after a dose of a GBCA [33]. Gd has also been seen in biopsy specimens of patients with NSF, when scanning electron microscopy/energy dispersive X-ray spectroscopy were employed [34, 35]. Gd in tissue can also be quantified with the same technique [36] or with inductively coupled plasma mass spectrometry [37, 38]. Gd deposition in NSF-affected skin has been demonstrated, though it was not seen in skin not affected by NSF. The amount of Gd in the tissue also increases over time, suggesting that the bone acts as an initial reservoir for Gd and that, over time, the Gd is slowly released into the circulation to deposit finally into the tissue. This could explain the delayed onset of NSF after a dose of a GBCA has been given [36].

The measurements of Gd in tissue have been important in linking Gd to NSF. However, there are currently eight cases of NSF in the literature where a dose of a GBCA could not be documented, suggesting that, though Gd may markedly increase the risk of NSF, it may not be required [14, 17–22]. If Gd truly is required, then either the diagnosis of NSF in these publications was incorrect or the patient had a dose of a GBCA at a facility where it could not be documented. The latter is more likely, as all of these reports mention the inability to document no GBCA with 100% certainty. Nonetheless, eight cases are significant. Documentation of no Gd in these biopsy samples with the above techniques would be ideal, though the complexity and availability of these techniques is a limitation.

Pathogenesis

The association of NSF with GBCA and the finding of Gd in skin affected by NSF has created interest in Gd and the properties of GBCAs that could result in release of free Gd. Gd is a rare-earth element in the lanthanide group and has an atomic number of 64. It has a large number of unpaired electrons (seven) that make it more paramagnetic than other elements. Gd must interact with the protons of surrounding water molecules in order to generate contrast in magnetic resonance (MR) imaging by disturbing the relaxation of these protons in a magnetic field. Chelates were designed to bind Gd at eight of nine coordination sites. The ninth coordination site has to be left free for the Gd ion to interact with a water proton. This free coordination site is what allows Gd to dissociate from the chelate [39]. The chemical group attached to the chelate that interacts at these coordination sites determines the affinity of the chelate for Gd. Non–ionic groups tend to have less affinity than charged carboxyl groups, and this makes ionic chelates more stable than non-ionic chelates [40]. The stability of the Gd–chelate bond has been expressed as the thermodynamic stability (measured at a high pH) and conditional stability (measured at a pH of 7.4) [41]. If the GBCA were allowed to stay in solution indefinitely, these two stability constants would determine the final amount of free Gd that was eventually released.

Kinetic stability measures the ability of Gd to dissociate at a pH of 0.1 and is expressed as a half-life, with the longer half-life being more stable. This value determines how long it will take for a free Gd molecule to be released from its chelate. Because cyclic chelates bind Gd in a rigid ring, Gd must simultaneously break all its bonds with the chelate to be released. Flexible linear chelate bonds can be broken sequentially, resulting in a more rapid release of Gd [42]. Since NSF is seen only in patients with decreased renal function, with the risk increasing with worsening renal function, this stability constant is considered to be the most important. In patients with normal renal function the distribution and elimination of the GBCA are similar to those of water-soluble iodinated contrast media or inulin and are rapidly excreted by the kidney before they have time to dissociate into free chelates and free Gd. With the increased time in circulation with advancing renal failure, the chelates have enough time to dissociate. Less kinetic stability (shorter half-life), together with a prolonged time in circulation, has been used to explain why linear chelates are more likely to cause NSF than are cyclic chelates and also why NSF is seen more frequently as renal function declines. Peritoneal dialysis provides poor clearance of GBCAs [43], and the attack rate is 7.5-times higher in peritoneal dialysis patients than in hemodialysis patients exposed to a GBCA [22]. The GBCAs commercially available in Europe and the USA are listed in Table 3.

Based on the assumption that NSF is caused by release of free gadolinium into tissues, the above stability constants have been used to determine the risk of each GBCA to cause NSF. One drawback to this approach is that the stability constants for the GBCAs were measured by a variety of different investigators, and comparison of the values with one another makes the comparisons less reliable. Nonetheless, from these data, the risk of releasing Gd and therefore causing NSF has been determined to follow this order: non-ionic linear chelates > ionic linear

Table 3 Properties of GBCAs. All are approved for use in Europe. *Kinetic stability* is the half-life for dissociation of the GBCA into free Gd and chelate

Generic name	Trade name	Structure	Charge	FDA approved?	Kinetic stability [39, 72]
gadodiamide	Omniscan	Linear	Non-ionic	Yes	35 seconds
gadoversetamide	OptiMARK	Linear	Non-ionic	Yes	Not available
gadopentetate dimeglumine	Magnevist	Linear	Ionic	Yes	10 minutes
gadobenate dimeglumine	MultiHance	Linear	Ionic	Yes	Not available
gadoxetic acid disodium	Primovist	Linear	Ionic	No	Not available
gadofosveset trisodium	Vasovist	Linear	Ionic	No	Not available
gadoteridol	ProHance	Cyclic	Non-ionic	Yes	3 hours
gadobutrol	Gadovist	Cyclic	Non-ionic	No	24 hours
gadoterate meglumine	Dotarem	Cyclic	Ionic	No	>1 month

chelates > non-ionic cyclic chelates > ionic cyclic chelates [39].

This theory is supported by the frequency of the reported cases. Gadoversetamide and gadodiamide both have a linear chelate that bind Gd, and both compounds are non-ionic. Gadodiamide and gadoversetamide have equivalent thermodynamic and conditional stabilities. The kinetic stability for gadoversetamide is not known, but it is the shortest for gadodiamide at 35 s, in comparison with greater than 1 month for gadoterate meglumine (cyclic ionic chelate) [42]. Based on these values and the theory that Gd release is the cause of NSF, then gadodiamide and gadoversetamide should have the highest risk of causing NSF. Gadodiamide features in the largest number of published case reports and the largest number of cases reported to the FDA. The small number of reported cases for gadoversetamide can be explained by the small market share. An estimate of the US market, share using Veterans Affairs purchasing records, shows that gadoversetamide had only 6% of the market share compared with 54% for gadopentetate dimeglumine and 26% for gadodiamide between 2005 and 2007. Gadoversetamide was not approved for use in Europe until 23 July 2007 [44]. The overwhelming majority of cases reported for gadodiamide cannot be explained by market share when it is compared with gadopentetate dimeglumine. However, the market share can explain the low incidence of gadoversetamide in the literature. Reporting bias and publication bias need to be considered when either published case reports or voluntary case reports are being reviewed.

Non-GBCA risk factors for NSF

All cases of NSF have occurred in patients with decreased renal function, whether it was acute kidney injury or chronic kidney disease. Sadowski et al. reported a series of patients with NSF in which two of those patients had an estimated glomerular filtration rate (eGFR) based on a creatinine measurement of greater than 30 ml/min per 1.73 m^2 body surface area at the time they received a GBCA. One patient had received a renal transplant and the other had received a liver transplant, and both had acute kidney injury. They were listed as having chronic kidney disease (CKD) stage III [45]. In response to that article, the FDA updated its original warning from a GFR of less than 15 ml/min per 1.73 m^2 as the cutoff for at-risk patients to a GFR of less than 60 ml/min per 1.73 m^2. Criticisms of the Sadowski et al. paper included the argument that a GFR cannot be reliably calculated using creatinine in the setting of acute kidney injury and that the true GFRs of renal and liver transplant recipients are typically lower then the eGFRs using creatinine [46]. In response, the FDA again changed the GFR value to less than 30 ml/min per 1.73 m^2 (CKD stage IV) as the cutoff for patients at risk who receive a GBCA [47].

Other risk factors for NSF, besides decreased renal function and receiving a GBCA, have been evaluated but have had less significance. Acidosis was suggested in early reports [48] but was not substantiated in later reports [49]. Many patients have increased incidence of thrombosis, and markers of increased risk for thrombosis have been found in patients with NSF, such as elevated antiphospholipid and anticardiolipin antibodies; deficient proteins C, S, and antithrombin III levels, and presence of factor V Leiden [4, 8, 50–52]. Increased inflammation associated with major surgery or infection has also been suggested as an additional risk factor [45]. Patients with hepatorenal disease or in the perioperative liver transplantation period have an increased risk, based on the number of reported cases of these patients [29, 45]. The true GFR in these patients is typically much lower than the eGFR would suggest, and they typically have an excess burden of inflammation. Erythropoietin use has also been associated with NSF [53], but anemia of chronic disease with erythropoietin resistance may be a marker of these patients' inflammation. These additional risk factors come from a variety of anecdotal case reports or small retrospective series.

The most successful treatment of NSF has been recovery of renal function with recovery of acute kidney injury or transplantation. However, even transplantation has not resulted in improvement in all cases [3]. Many other treatments have been tried, and there are many anecdotal reports of success. As expected, corticosteroid steroids have been tried, but have had little success [54, 55]. Next to improvement in renal function, extracorporeal phototherapy has had the most success in the literature [56–58]. Other treatments that have been tried are listed in Table 4.

Prevention

The key to prevention is to avoid administration of a GBCA to patients at increased risk. In the past, GBCAs were considered not to be nephrotoxic, and the doses escalated. As the doses increased, it became evident that GBCAs are nephrotoxic [28, 59]. Gd is less radio-dense than iodine is, and higher doses are required to produce the same attenuation on standard X-ray imaging [60]. It was common practice in the past to use a GBCA as a replacement for iodinated contrast media in patients with CKD, to avoid nephrotoxicity. The dose used for this indication, in practice, was as high as 0.9 mmol/kg [61]. However, the use of a GBCA as a replacement for iodinated contrast agents in standard X-ray angiography has never been approved, either in Europe or in the USA. The highest dose approved for use in Europe is 0.3 mmol/kg for MR angiography. The highest dose approved by the FDA is 0.1 mmol/kg as an initial dose followed by 0.2 mmol/kg 20 min later if the first dose is not adequate for imaging. The FDA has not approved the indication for MR angiography. The FDA has not approved the use of any GBCA for children under the age of 2 years [47].

The need for Gd to enhance an MR image is not standardized and is usually dependent on the preference of the radiologist and perhaps the sub-specialist requesting the examination. When transplant kidneys were imaged by MR imaging, there was an improvement in the clarity of the findings with Gd-enhanced contrast, but diagnostic results were not statistically different [62]. In the evaluation of pediatric renal disease, MR urography with Gd enhancement was superior in non-dilated collecting systems, equivalent in the assessment of obstructed but normal functioning upper urinary tracts, and inferior in the assessment of non-functioning dilated collecting systems and multicystic dysplastic kidneys, when compared with non-enhanced imaging [63]. This allows one to make the argument that all imaging, including non-contrasted MR imaging, should be performed and evaluated first before one proceeds with an MR examination with a GBCA in patients at high risk for NSF.

The use of dialysis to remove the GBCA before it releases free Gd has been recommended as prevention for NSF. This is based on data regarding the clearance of Gd with hemodialysis. One study showed the disappearance of 98.9% of Gd from the serum after three sessions of hemodialysis. However, the dialysate was not collected after the first session, so it is unclear if the disappearance from the serum was from removal by dialysis or deposition into the tissue [64]. Broome et al. had four cases of NSF that developed even after daily dialysis for 3 days in a row. The time between the patients' receiving the GBCA and the time of dialysis was 9 h, 17 h, 18 h and 21 h in the four cases. It is possible that dialysis might be beneficial if started sooner than 9 h, but there is no direct evidence that hemodialysis is effective in preventing NSF [29, 65]. The problem with recommending prompt hemodialysis after administration of a GBCA is that physicians may have a false sense of security with the use of hemodialysis as prevention. Peritoneal dialysis clears GBCAs very poorly with a half-life of 52.7 h [43]. Consistent with the theory that prolonged circulation allows more release of free Gd into tissue, the risk of NSF is highest in peritoneal dialysis, with an attack rate 7.5-times higher than that in hemodialysis patients if a GBCA had been administered [17].

Recommendations

There are recommendations from many sources regarding NSF. The Pharmacovigilance Working Party (PhVWP) is a division of the European Medicines Agency that makes recommendations regarding monitoring of medicinal products on the European market, and the FDA regulates drug usage in the USA. The FDA and the PhVWP have given recommendations that should be reviewed. The FDA, as mentioned above, has twice changed the value of GFR for patients considered to be at risk. The GFR was originally 15 ml/min per 1.73 m^2, then 60 ml/min per 1.73 m^2 and, currently, is 30 ml/min per 1.73 m^2. The FDA does not point to a specific GBCA as carrying more risk than any other in the at-risk patients and does not state that any

Table 4 Treatments for NSF

Treatment of NSF
Extracorporeal phototherapy [56–58]
Ultraviolet A1 [73, 74]
Plasmapheresis [75]
Sodium thiosulfate [76]
Intravenous therapy with immunoglobulin [77]
Corticosteroids [54, 55]

GBCA has a contraindication. Instead, the recommendation is for the physician to consider carefully the use of any GBCA in at-risk patients. The FDA also includes patients with any decrease in renal function, with the hepatorenal syndrome a risk as well as any patient in the perioperative liver transplant period, regardless of the level of kidney function. Prompt hemodialysis is recommended after an at-risk patient has received a GBCA, but prompt is not defined. Since the FDA has not approved the use of any GBCA in children less than 2 years of age, there is no warning about the use in infants.

In contrast to the FDA, the PhVWP separates the various GBCAs based on their charge and structure [66]. Both gadodiamide and gadoversetamide contain linear non-ionic chelates, and gadopentetate dimeglumine contains a linear ionic chelate. The PhVWP states that these three GBCAs are contraindicated in patients with a GFR of <30 ml/min per 1.73 m^2 and should be used with caution in patients with a GFR between 30 ml/min per 1.73 m^2 and 59 ml/min per 1.73 m^2. These recommendations are based on the number of reported cases for gadopentetate dimeglumine and gadodiamide and the charge and structure of gadoversetamide and gadodiamide. Gadodiamide is the only GBCA contraindicated in patients with or about to undergo liver transplantation. Gadoversetamide is not approved for children under the age of 2 years, since it has not been studied in this age group. Since gadodiamide and gadopentetate dimeglumine have been approved for use in this age group, there is a warning that the use in infants less than 1 year of age be carefully considered because of immature renal function. However, this is only a theoretical risk, because the youngest reported patients were 8 years of age [3–5].

The rest of the GBCAs include those with a linear ionic chelate (except gadopentetate dimeglumine) and those with a cyclic chelate. The PhVWP states that the cyclic chelates should be safer, based on structure, but there is no difference in the product warning labels for these agents. These agents all have the same generic warning stating that they should be used with caution in patients with a GFR of <30 ml/min per 1.73 m^2. There are no groups of patients that have contraindications for the use of these GBCAs. There is no warning regarding the use of these agents in infants [66].

Conclusion

NSF is a new disease with a strong, though not absolute, association with GBCAs. NSF was first seen in 1997, which corresponds to the time that GBCAs were increasing in both use and dose. If there were earlier cases of NSF not associated with Gd, they may have been misdiagnosed because of the rare occurrence of the disease and the frequent skin and joint problems of dialysis patients. Erythropoietin may also increase the risk, though the association is far less than with a GBCA. The dosing of erythropoietin has recently decreased, but it cannot be avoided in the treatment of dialysis patients. GBCAs, on the other hand, have been used for indications and doses that were not approved, and, in most patients at risk for NSF, they could be avoided. Gadodiamide produces the highest risk, based on reported cases and structure and charge, and should be avoided in any at-risk patient. The cyclic-based GBCAs may produce a decreased risk and should be used in patients at risk for NSF if Gd enhancement is absolutely required. It is unlikely that there will be an adequate alternative for Gd in MR imaging, because of its unique paramagnetic properties. Instead, the development of Gd-chelates with an improved kinetic stability may, again, make contrast-enhanced MR imaging safe for patients with decreased renal function.

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