Cancer Imaging (2007) **7**, 130–137
DOI: 10.1102/1470-7330.2007.0019

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ARTICLE

Nephrogenic systemic fibrosis (NSF): a late adverse reaction to some of the gadolinium based contrast agents

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Data accepted for publication 23 July 2007

Abstract

Until recently it was believed that extracellular gadolinium based contrast agents were safe for both the kidneys and all other organs within the dose range up to 0.3 mmol/kg body weight. However, in 2006, it was demonstrated that some gadolinium based contrast agents may trigger the development of nephrogenic systemic fibrosis, a generalised fibrotic disorder, in renal failure patients. Accordingly, the use of gadodiamide and gadopentate dimeglumine for renal failure patients was banned in Europe in spring 2007. The same two compounds should only be used cautiously in patients with moderate renal dysfunction. The current paper reviews the situation (July 2007) regarding gadolinium based contrast agent and the severe delayed reaction to some of these agents. The fear of nephrogenic systemic fibrosis should not lead to a denial of a well indicated enhanced magnetic resonance imaging examination.

Keywords: *Gadolinium based contrast agents; late adverse reactions; nephrogenic systemic fibrosis.*

Introduction

Magnetic resonance imaging (MRI) contrast media are used to improve visualisation of abnormal structures or lesions in various parts of the body. The most common MRI contrast media are based on paramagnetic compounds that contain metal ions from the transition or lanthanide series of the periodic table such as manganese, iron and gadolinium. These metal ions have a large magnetic moment and can shorten the longitudinal (T1) and transverse (T2) relaxation times of protons in the water of tissues. The lanthanide metal ion gadolinium has the strongest effect of all elements on T1 relation time because it has seven unpaired electrons. Gadolinium alone is highly toxic in vivo because it is distributed to bone, lymph nodes and the liver, where it rapidly produces liver necrosis. It obstructs calcium ion passage through muscle cells (reducing neuromuscular transmission), and interferes with intracellular enzymes and cell membranes by the process of transmetallation, a phenomenon whereby Gd^{3+} replaces endogenous metals such as zinc and copper. To prevent the harmful effects of Gd^{3+}, and make it usable in humans, Gd^{3+} needs to sequestered by non-toxic substances. At the same time its contrast enhancement must be maintained. These two goals are achieved by binding Gd^{3+} to another agent, known generally as a 'chelate'. Chelates are large organic molecules that form a more or less stable complex around the Gd^{3+}. The gadolinium ion has nine coordination sites, of which eight are used for binding with the chelate. The various gadolinium chelates have different physico-chemical properties (Table 1), including bonds between the gadolinium atom and the ligands which are of different stability. Bonds between carboxyl groups and amino nitrogen atoms and the gadolinium ion are the strongest, whereas bonds involving amide carbonyl atoms are the weakest.

Since early 2006 evidence has accumulated that some gadolinium based contrast agents, particularly

1470-7330/07/000001 + 08

Table 1 The various gadolinium based agents

Brand name	Generic name	Acronym	Chemical structure	Charge	Elimination pathway	Protein binding	Cases of NSF*
Omniscan	Gadodiamide	Gd-DTPA-BMA	Linear	Non-ionic	Kidney	None	Yes
OptiMARK*	Gadoversetamide	Gd-DTPA-BMEA	Linear	Non-ionic	Kidney	None	Yes
Magnevist	Gadopentetate dimeglumine	Gd-DTPA	Linear	Ionic	Kidney	None	Yes
MultiHance	Gadobenate dimeglumine	Gd-BOPTA	Linear	Ionic	97% kidney, 3% bile	<5%	No
Primovist	Gadoxetic acid disodium salt	Gd-EOB-DTPA	Linear	Ionic	50% kidney, 50% bile	<15%	No
Vasovist	Gadofosveset trisodium	Gd-DTPA	Linear	Ionic	91% kidney, 9% bile	>85%	No
ProHance	Gadoteridol	Gd-HP-DO3A	Cyclic	Non-ionic	Kidney	None	No
Gadovist	Gadobutrol	Gd-BT-DO3A	Cyclic	Non-ionic	Kidney	None	No
Dotarem	Gadoterate meglumine	Gd-DOTA	Cyclic	Ionic	Kidney	None	No

*Unconfounded

gadodiamide (Omniscan®, GE Healthcare, Chalfont St. Giles, UK), may cause a potentially devastating or even fatal scleroderma-like, fibrosing condition called nephrogenic systemic fibrosis (NSF) in patients with renal failure[1–10]. Recently it has been shown that gadopentetate dimeglumine (Magnevist®, Bayer Schering, Berlin, Germany) may also trigger NSF, but apparently not with the same high frequency as gadodiamide. The European Medicines Agency has decided that the use of both agents in patients with a glomerular filtration rate below 30 ml/min per 1.72 m^2 (CKD 4 and 5) is contraindicated and that they should be used only with caution in patients with moderately reduced kidney function (30–60 ml/min per 1.72 m^2 (CKD 3)). In the USA cases of NSF have been reported after exposure to gadoversetamide (OptiMARK®, Covidien, St. Louis, USA). NSF has not been reported after gadoterate meglumine, gadoteridol, gadobenate dimeglumine or gadobutrol. Some of these agents have been used in many patients in imaging departments serving nephrology centres. However, an absence of reports does not mean that it is impossible that they could induce NSF, but rather suggests that the risk is significantly lower than for example after gadodiamide. In this review the current situation (July 2007) is presented.

NSF

NSF was first described in San Diego, California, USA, in 1997 as an idiopathic skin condition characterized by thickening and hardening of the skin of the extremities and sometimes the trunk, with an increase in the number of dermal fibroblast-like cells associated with collagen remodelling and mucin deposition.

The typical patient is middle-aged and has end-stage renal disease (ESRD). Most, but not all, reported patients are on regular dialysis treatment. The first signs of NSF may be seen within hours of exposure to gadolinium based contrast agents, but may occur as late as 3 months after exposure. Typically, the condition begins with subacute swelling of distal extremities followed in subsequent weeks by severe skin induration and sometimes extension to involve the thighs, forearms, and lower abdomen. The skin induration may be aggressive and associated with constant pain, muscle restlessness, and loss of skin flexibility. In some cases, NSF leads to serious physical disability including becoming wheelchair bound. For many patients, the skin thickening inhibits the flexion and extension of joints, resulting in contractures. Those severely affected may be unable to walk or fully extend the upper and lower limb joints. Complaints of muscle weakness are common, and deep bone pain in the hips and ribs has been described. Radiography may show calcification of soft tissue.

NSF was initially observed in and thought to affect the skin only, so it was called nephrogenic fibrosing dermopathy (NFD), but it is now known that it may involve organs such as the liver, lungs, muscles and heart. Involvement of internal organs may explain the suspected increased mortality of NSF patients. About 50% of patients have a progressive severe disease course. NSF may contribute to death by causing scarring of body organs (which impairs normal function), by restricting effective ventilation, or by restricting movement leading to falls which may cause fractures or haemorrhage. Other patients have died as a result of renal disease or transplant surgery. Eighteen month mortality was increased significantly as compared to those without NSF (40% versus 16%, respectively), with an adjusted hazard ratio of 2.9 (95% CI 1.3–6.5), $p = 0.008$) in one study from Boston. However, it is difficult in this high-risk group to differentiate deaths due to complications of the underlying disease and its treatment from those due to NSF.

In several studies the incidence of NSF after exposure to gadodiamide has been reported to be between 3 and 7% in patients with reduced renal function. In CKD 5 patients (GFR less than 15 ml/min per 1.72 m^2) it may be closer to 20%. The incidence after gadopentetate dimeglumine and gadoversetamide is unknown. Only one centre has reported a large number (>10) of NSF cases after gadopentetate dimeglumine, whereas many centres, including our own, have reported more than 10 cases after gadodiamide. This difference is not just a reflection of the market share of the two products because gadopentetate dimeglumine has been administered to as many as 4–5 times the number of patients that have had gadodiamide.

Diagnosis is confirmed by the presence of specific histopathological features on deep skin biopsy, which is a prerequisite for the definite diagnosis of NSF. It is extremely important to differentiate NSF from other fibrosing skin disorders. Histology shows infiltration with dermal spindle cells, which are characterised by the surface markers CD45RO, CD34 and Procollagen I. These cells have an immunologic profile which is identical to circulating fibrocytes, which are known to participate in normal wound healing. When there is tissue injury, these cells infiltrate the injured tissues and are involved in wound healing and scar formation. In NSF, these cells enter uninjured tissue. Renal impairment may be involved in the malfunction of these cells. Other typical features of NSF are plumped collagen bundles, mildly increased interstitial mucin deposition and absence of inflammation.

Validation of NSF cases

Because NSF may mimic other skin lesions that occur in patients with end-stage renal failure, the diagnosis of NSF should never be made without a histological evaluation by an experienced dermatopathologist.

Correlation of the disease to exposure to drugs or contrast media requires adequate documentation of what the patient has been exposed to. Not all radiology departments have an adequate registration system for the dose and name of the contrast medium used. Sometimes nicknames are used independent of the product used as well as continuation of use of the brand-name, despite the fact that a new vendor has been introduced. Also the patients' weight is often not recorded. The lack of a complete record causes problems in retrospective studies which we have found in trying to detect unsuspected NSF cases. In the future it is very important that a record is always kept of the type and amount of each injection of gadolinium based contrast agent given and that all new cases of NSF are reported to the appropriate National Regulatory Authority. Interestingly, no National Medicines Agency had any record of NSF when we submitted the first 20 cases to the Danish Authorities in March 2006. The authorities only need four simple facts: (1) initials, birth date and sex of the patient; (2) the adverse event; (3) name of the drug; and (4) name of the reporting person including occupation. When this information is submitted it counts as a report in Europe, but it does not prove the presence of NSF. The information requires validation, which is the responsibility of the vendor.

Validation becomes even more difficult when several gadolinium products have been used in a short period of time. Thus, if two different gadolinium based contrast media have been injected within 8 weeks of each other (maybe longer), it is impossible to determine with certainty which agent triggered the development of NSF and the situation is described as 'confounded'. However, the agent which is most likely to be responsible is the one which has triggered NSF in other unconfounded situations.

Co-factors in the development of NSF

Time has shown that two factors are important: (1) reduced renal function and (2) exposure to one of the less stable gadolinium based contrast agents. The severity of NSF may correlate with the dose that patients have been exposed to over time, but cases have also developed after a single 0.1 mmol/kg standard dose. Also, NSF does not develop in all at-risk patients after exposure to the less stable gadolinium based contrast agents. Therefore many investigators had been looking for co-factors that may destabilise the agent.

The following co-factors have been suggested: high doses of EPO, metabolic acidosis, iron and ferritin, chronic inflammation, hypercoagulability, thrombotic events, recent vascular surgery, recent renal transplant failure, recent surgery, anion gap, or increased phosphate. However, no universal co-factor apart from renal failure has been identified. Marckmann *et al*. could not identify any exposure/event other than gadodiamide common to more than a minority of the patients who developed NSF. The Center for Disease Control and Prevention found that only exposure to gadolinium containing CM during the preceding 6 months or preceding year remained statistically significant in their case–control study of 19 NSF cases.

Our current knowledge suggests that there may be several co-factors that increase the risk of NSF after some gadolinium based CM. However, some of the factors may have been listed just by chance because enhanced MRI was performed when the particular factors were present. For example, in some departments enhanced MRI is done as part of the evaluation of thrombo-embolic symptoms, post surgical complications, etc., whereas in other departments MRI is not used in those situations. Therefore, one institution may report that NSF occurs more frequent in patients with particular conditions, but others cannot confirm it because they use enhanced MRI for different indications.

At the University of Copenhagen, where the highest number of European NSF cases has been collected (27 cases as of July 2007), gadodiamide enhanced MRI was mainly used as a part of pretransplant work-up. This group of patients only had signs and symptoms related to their uraemia, leading us to question some of the 'surgical' co-factors. Indications for the examinations should always be given, when possible co-factors are being sought as they may bias the results. The same applies to whether or not NSF patients were on dialysis. Haemodialysis is said to predispose to NSF, but it could just be the fact that patients undergoing haemodialysis have more vascular problems requiring enhanced MRI for evaluation than patients on continuous peritoneal

dialysis or on conservative therapy. At the University of Copenhagen 60% of the patients who developed NSF were not on haemodialysis.

Registries

During the last year many registries have collected data about NSF cases and this leads to confusion. The International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR, http://www.icnfdr.org) has collected cases of NSF submitted to them since 2000. Most cases are American and a case can only registered if the head of the registry, Dr Shawn Cowper, has evaluated the histologic specimen and agrees with the diagnosis of NSF. Since June 8th, 2007 the FDA has encouraged reporting of American cases through Med-Watch. The cases are not validated and many do not fulfil the criteria mentioned above or the criteria for being included in the International Registry. Nonetheless, the figures are quoted frequently. The same applies to the reports submitted to National Regulatory Authorities in the various European countries, all of which rely on the vendor to collect the validating data. Both the Contrast Media Committee of American College of Radiology and the European Society of Urogenital Radiology have asked their members to report cases, but these again are not validated. Also the vendors have a registry, which should be identical to that of the National Regulatory Authorities. Finally, there is the peer-reviewed literature, which provides the most reliable information, but suffers from delays in the collection of data and the publication process. By March 12, 2007, a total of 74 cases had been reported in the literature. Seventy-two had had gadodiamide, one had gadopentetate and in one no exposure could be verified.

Transmetallation

All available gadolinium contrast agents are chelates that contain the gadolinium ion (Gd^{3+}). There are two structurally distinct categories: cyclic chelates (e.g. gadoteridol, gadobutrol and gadoterate meglumine), where Gd^{3+} is caged in a cavity, and linear chelates (e.g. gadodiamide and gadopentetate dimeglumine (Fig. 1)). For some gadolinium contrast agents (e.g. gadodiamide and gadoversetamide), excess chelate is included in the contrast-agent preparation to ensure the absence of toxic free gadolinium (Gd^{3+}) in solution. High chelate concentration is an indirect marker of the likelihood that free gadolinium will be released more easily from the chelate complex. Some gadolinium-based contrast media, e.g. gadodiamide, are more likely than others to release free Gd^{3+} through a process called transmetallation with endogenous ions from the body. Also, transmetallation may occur more readily when a gadolinium contrast agent remains inside the body for a long period, as occurs in patients with renal failure.

Cyclic molecules offer better protection and binding to Gd^{3+} than do linear molecules. For example, the ionic cyclic chelate gadoterate meglumine has a much longer dissociation half-life and higher thermodynamic stability than the non-ionic chelate gadodiamide. Cyclic chelates (e.g. gadoteridol, gadobutrol, and gadoterate meglumine) need no excess chelate to ensure the absence of toxic

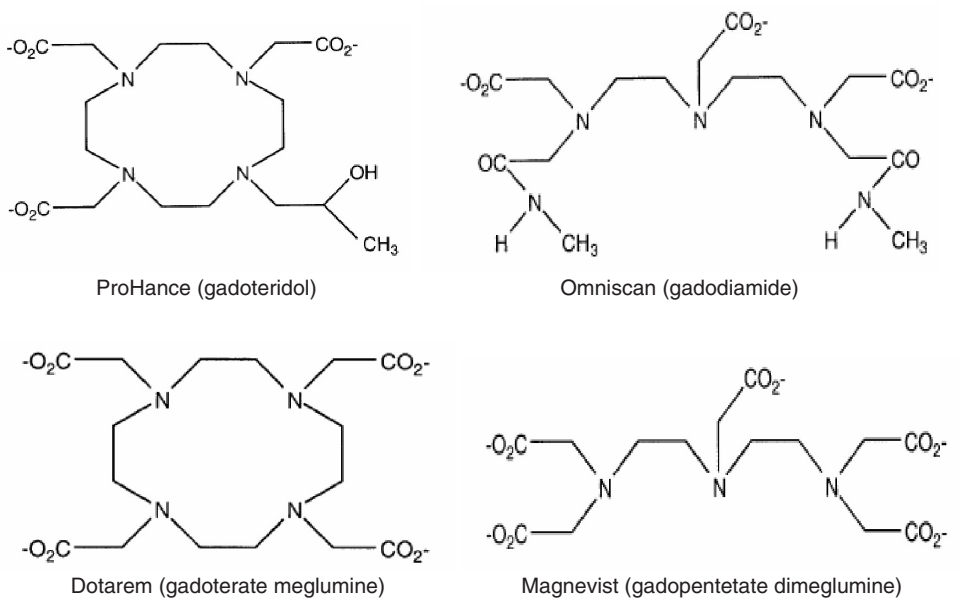

Figure 1 **Principle chemical structures of the various gadolinium based contrast agents. Examples: cyclic chelates, non-ionic (ProHance [gadoteridol]) and ionic (Dotarem [gadoterate meglumine]); linear chelates, non-ionic (Omniscan [gadodiamide]) and ionic (Magnevist [gadopentetate dimeglumine]).**

Gd^{3+} in solution and are least likely to release free Gd^{3+} from the chelate complex.

All gadolinium-based agents are to some degree excreted by the kidneys, varying from 50% for gadoxetate disodium (with 50% hepatic elimination) to 100% for most other agents (see Table 1). The excretion pathway is especially important for patients with renal dysfunction. Other unique pharmacokinetic properties may also have a contributory role. For example, gadofosveset trisodium has a prolonged serum half-life due to its unique binding properties to serum albumin.

Gadodiamide underwent more transmetallation than did two other gadolinium-containing contrast media (gadoteridol and gadopentetate dimeglumine) in healthy volunteers. Gadoteridol was found to be the most inert of the three drugs tested. Moreover, gadodiamide administration to patients resulted in the highest increase of zinc in urine (which suggests transmetallation) compared with two other gadolinium-containing contrast media (gadoterate meglumine and gadopentetate dimeglumine). Also, transient increases in serum iron levels after injection of gadodiamide have been reported.

Gadolinium deposition occurs in human body tissues and has been identified in tissue samples from patients with NSF up to 11 months after exposure to gadodiamide. No gadolinium was identified in tissue from a patient without NSF. Other metals found in the tissue of NSF patients included large deposits of iron, copper, and zinc. Gadolinium in the tissue samples is associated with cell bodies and gadolinium may therefore be phagocytosed by macrophages. Intracellular gadolinium may increase the number of profibrotic cytokines or growth factors, leading to dermal or systemic fibrosis. Gadolinium deposition in patients with NSF may be restricted to areas where there was also deposition of calcium phosphate. Cutaneous gadolinium deposition may have a role in the development of NSF.

Why did it take so long to connect gadolinium contrast media and NSF?

It took nearly 9 years from the diagnosis of the first NSF case to the recognition that the disease was associated with exposure to the less stable gadolinium based contrast agents. There are many good reasons for this. Uraemic patients are exposed to many drugs and the drugs change during the progress of their disease. Generally contrast agents, in particular MR agents, have been considered safe inert drugs. NSF is a delayed reaction that mainly occurs weeks after the patient has received the contrast medium. It does not occur in all CKD 5 patients (GFR less than 15 ml/min per 1.72 m^2) and to date has only occurred after the less stable gadolinium based contrast agents. Access to MRI has increased considerably since the beginning of the century and new techniques such as step-wise angiography based on a single contrast injection are now available. Until recently most physicians did not know about NSF. Mild changes, for example on the legs, may have gone undiagnosed and only severe changes which have led to significant disability have been noticed. With all these circumstances it is not surprising that it took a time for the connection to be recognised.

Patients at risk

Patients at higher risk are those with CKD 4 and 5 (GFR <30 ml/min), those on haemo- or peritoneal dialysis and patients with reduced renal function who have had or are awaiting liver transplantation. Patients at lower risk are those with CKD 3 (GFR 30–59 ml/min) and children under 1 year, because of their immature renal function. To date, no cases where the patient had normal renal function, CKD 1 and 2 (GFR >60 ml/min per 1.72 m^2), have been reported in the literature.

Determination of glomerular filtration rate

Accurate determination of the glomerular filtration rate is not easy. The most precise method is the inulin clearance, and isotope methods give similar results. However, both methods are cumbersome and impractical for daily use. Measurement of serum creatinine is not satisfactory because more than 25% of older patients have normal serum creatinine levels but reduced glomerular filtration rates. A single determination of the glomerular filtration rate does not exclude acute renal insufficiency.

Renal function can also be estimated using specially derived predictive equations. The most accurate results are obtained with the Cockroft–Gault equation, whereas the most precise formula is the Modification of Diet in Renal Disease (MDRD) study equation. Unfortunately, the predictive capabilities of these formulae are suboptimal. In addition, they are not useful for patients with a glomerular filtration rate above 60 ml/min. Even below this level they do not always result in the same glomerular filtration rate. For instance a 43-year-old 70-kg male patient with a creatinine level of 132 μmol/l has a glomerular filtration level of 63 ml/min if it is calculated by the Cockcroft–Gault equation. The same patient will have a glomerular filtration level of 66 ml/min if he is Afro-American and 54 ml/min if he is Caucasian, if it is calculated by the MDRD equation. If he had been Asian, the glomerular filtration level would have been even lower, but there are no established equations for Asians. Had the glomerular filtration in all instances been 30 ml/min lower, it would have been illegal to use gadodiamide in the Caucasian and the Asian if the glomerular filtration rate had been estimated according to the MDRD equation, but not if it had been estimated according to the Cockcroft–Gault. Which figure is the correct one?

In practice, it is easier to use one of the more stable gadolinium agents, for which glomerular filtration rate measurement before administration is not mandatory.

Laboratory analyses

Gadodiamide interferes with the technique of measurement of serum calcium commonly used in hospitals. Cases of spurious hypocalcaemia caused by the formation of a complex between Gd^{3+} and a reagent (*o*-cresol-phthalein, OCP) used in the measurement technique have been reported with gadodiamide and gadoversetamide. As a general rule, laboratory measurements on blood and urine should not be performed within 24 h of administration of any contrast medium.

Special precautions for cancer patients

No special factors related to cancer patients have been identified. If they have renal impairment, the same recommendations as for other patients should be followed. The easiest and safest recommendation seems to be to choose a gadolinium agent not associated with NSF to date. One should never deny a cancer patient enhanced MRI if there is a good clinical indication.

Alternative imaging

There are several conditions where alternative imaging cannot replace enhanced MRI because it is inferior diagnostically. The risk of NSF is low if the non-ionic linear chelates are avoided, and if only small doses of the stable agents are used in at-risk patients. It is important to recognize that the morbidity of haemodialysis in a patient not adjusted to haemodialysis is higher than the risk of NSF after exposure to a macrocyclic gadolinium agent. The risk of complications (procedural, allergy-like reactions, contrast induced nephropathy, radiation) following conventional or computed tomography (CT) arteriography with iodinated contrast medium must also be weighed carefully against performing MR using a stable gadolinium agent.

Conclusion

NSF is an important delayed adverse reaction to some less stable gadolinium based contrast agents. Concerns about NSF however should not have the undesirable consequence that we do not diagnose or monitor significant disease properly. Stable gadolinium based contrast agents not associated with NSF to date can be used. Of course, any imaging procedure should only be undertaken after careful consideration of its benefits and risks, but that was also the case before NSF was recognised. An overview is given in Table 2.

Table 2 Overview of nephrogenic systemic fibrosis

Definitions	
Unconfounded	In 'unconfounded' cases only one Gd-CM had been given before NSF developed
Confounded	If two different Gd-CM were injected within 8 weeks of each other (maybe longer), it is impossible to determine with certainty which agent triggered the development of NSF and the situation is described as 'confounded'. However, the agent that is most likely responsible is the one which has triggered NSF in other unconfounded situations.
Triggering agent	To be described as an NSF triggering agent, there must be at least 5–10 NSF cases, validated by adequate documentation including deep skin biopsy, following exposure to a Gd-CM
Chronic kidney disease (CKD)	CKD 1: GFR >90 ml/min per 1.73 m^2 CKD 2: GFR 60–90 ml/min per 1.73 m^2 CKD 3: GFR 30–60 ml/min per 1.73 m^2 CKD 4: GFR 15–30 ml/min per 1.73 m^2 CKD 5: GFR <15 ml/min per 1.73 m^2 and/or peritoneal or haemodialysis
Clinical features of NSF	
Onset	From the day of exposure for up to 2–3 months
Initially	Pain, pruritus, swelling, erythema, usually starts in the legs
Later	Thickened skin and subcutaneous tissues – 'woody' texture and brawny plaques; fibrosis of internal organs, e.g. muscle, diaphragm, heart, liver, lungs
Result	Contractures, cachexia, death in a proportion of patients
At-risk patients	
Higher risk	Patients with CKD 4 and 5 (GFR <30 ml/min); patients on dialysis; patients with reduced renal function who have had or are awaiting liver transplantation
Lower risk	Patients with CKD 3 (GFR 30–59 ml/min); children under 1 year, because of their immature renal function

Serum creatinine measurement before gadolinium contrast media administration

– Approximately 40–50% of MRI patients receive Gd-CM
– The percentage of patients with CKD 3, 4 and 5 varies in different institutions
– Serum creatinine and estimated GFR (eGFR) are not always very accurate indicators of true GFR.
– In particular, acute renal failure may not be indicated by a single eGFR value
– Measurement of serum creatinine/eGFR is mandatory before Gd-CM which has been associated with subsequent development of NSF
– Measurement of serum creatinine/eGFR is not necessary in all patients receiving Gd-CM

Table 2 Contd.

Use of gadolinium contrast media	
General points	The risk of inducing NSF must always be weighed against the risk of denying patients gadolinium enhanced scans which are important for patient management In patients with impaired renal function, liver transplant patients and neonates, the benefits and risks of gadolinium enhancement should be considered particularly carefully In patients with CKD 4 and 5 (<30 ml/min): always use the smallest possible amount of the contrast agent to achieve an adequate diagnostic examination; never use more than 0.3 mmol/kg of any Gd-CM; never use gadolinium as a contrast agent for radiography, computed tomography, or angiography as a method of avoiding nephropathy associated with iodinated contrast media
Choice of gadolinium agent	
There are differences in the incidence of NSF with the different Gd-CM, which appear to be related to differences in physico-chemical properties and stability. Macrocyclic gadolinium chelates, which are pre-organised rigid rings of almost optimal size to cage the gadolinium ion, have high stability. Current knowledge about the properties of the different agents, and the incidence of NSF when they are used in risk patients are summarized below. Products are presented in alphabetical order according to their generic names	
Gadobenate dimeglumine (Multihance®)	
Ligand	Ionic linear chelate (BOPTA)
Incidence of NSF	No unconfounded* cases have been reported
Special feature	Similar diagnostic results can be achieved with lower doses because of its 2–3% protein binding
S-creatinine (eGFR) measurement	Not mandatory
Gadobutrol (Gadovist®)	
Ligand	Non-ionic cyclic chelate (BT-DO3A)
Incidence of NSF	No unconfounded* cases have been reported
S-creatinine (eGFR) measurement	Not mandatory
Gadodiamide (Omniscan®)	
Ligand	Non-ionic linear chelate (DTPA-BMA)
Incidence of NSF	3–7% in at-risk subjects
S-creatinine (eGFR) measurement	Mandatory
Haemodialysis	Gadodiamide is contraindicated in patients on dialysis
Contraindicated	Patients with CKD 4 and 5 (GFR <30 ml/min), including those on dialysis Patients with reduced renal function who have had or are awaiting liver transplantation
Use with caution	Patients with CKD 3 (GFR 30–60 ml/min) Children less than 1 year old
Gadofosveset trisodium (Vasovist®)	
Ligand	Ionic linear chelate (DTPA-DPCP)
Incidence of NSF	No unconfounded* cases reported, but experience is limited
Special feature	It is a blood pool agent with affinity to albumin. Diagnostic results can be achieved with 50% lower doses than extracellular Gd-CM. Biological half-life is 12 times longer than for extracellular agents (18 h compared to 1.5 h, respectively).
S-creatinine (eGFR) measurement	Not mandatory
Gadopentetate dimeglumine (Magnevist®)	
Ligand	Ionic linear chelate (DTPA)
Incidence of NSF	Estimated to be 0.1–1% in at-risk subjects
S-creatinine (eGFR) measurement	Mandatory.
Haemodialysis	Gadopentate dimeglumine is contraindicated in patients on dialysis
Contraindicated	Patients with CKD 4 and 5 (GFR <30 ml/min), including those on dialysis Patients with reduced renal function who have had or are awaiting liver transplantation
Use with caution	Patients with CKD 3 (GFR 30–60 ml/min) Children less than 1 year old
Gadoterate meglumine (Dotarem®)	
Ligand	Ionic cyclic chelate (DOTA)
Incidence of NSF	No unconfounded* cases have been reported
S-creatinine (eGFR) measurement	Not mandatory
Gadoteridol (Prohance®)	
Ligand	Non-ionic cyclic chelate (HP-DO3A)
Incidence of NSF	No unconfounded* cases have been reported
S-creatinine (eGFR) measurement	Not mandatory
Gadoversetamide (Optimark®) (this agent is not approved for use in Europe)	
Ligand	Non-ionic linear chelate (DTPA-BMEA)
Incidence of NSF	Unknown, but unconfounded* cases have been reported
S-creatinine (eGFR) measurement	Mandatory
Haemodialysis	Gadoversetamide is contraindicated in patients on dialysis
Contraindicated	Patients with CKD 4 and 5 (GFR <30 ml/min), including those on dialysis Patients with reduced renal function who have had or are awaiting liver transplantation
Use with caution	Patients with CKD 3 (GFR 30–60 ml/min) Children less than 1 year old

Continued.

Table 2 Contd.

Gadoxetate disodium (Primovist®)	
Ligand:	Ionic linear chelate (EOB-DTPA)
Incidence of NSF:	No unconfounded* cases have been reported but experience is limited
Special feature:	Organ specific gadolinium contrast agent with 10% protein binding and 50% excretion by hepatocytes. Diagnostic results can be achieved with lower doses than extracellular Gd-CM
S-creatinine (eGFR) measurement	Not mandatory

Immediate haemodialysis after administration of Gd-CM

At least 9 h of haemodialysis (3 sessions) is required to remove a Gd-CM. The efficacy of haemodialysis can be variable and depends on many factors. There is no evidence that immediate haemodialysis protects against NSF. In patients already being dialysed, it may be helpful to schedule the dialysis session after the gadolinium contrast examination. However, this is optional and should not cause delays in obtaining important diagnostic information. Initiating haemodialysis for the sole purpose of removing a Gd-CM is not recommended in patients who have not already been stabilised on haemodialysis as a replacement therapy. The procedure itself can be associated with significant morbidity, which is higher than the risk of inducing NSF with the most stable gadolinium agents

Nephrogenic systemic fibrosis (NSF), previously called nephrogenic fibrosing dermopathy, was described in 1997, but was only linked to exposure to gadolinium based contrast media (Gd-CM) in 2006.
*See definitions above.

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