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CONTRAST MEDIA

Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines

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Abstract
Purpose To update the guidelines of the Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) on nephrogenic systemic fibrosis and gadolinium-based contrast media.

Areas covered Topics reviewed include the history, clinical features and prevalence of nephrogenic systemic fibrosis and the current understanding of its pathophysiology. The risk factors for NSF are discussed and prophylactic measures are recommended. The stability of the different

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gadolinium-based contrast media and the potential long-term effects of gadolinium in the body have also been reviewed.

Key Points

- *Clinical features, risk factors and prevention of nephrogenic systemic fibrosis are reviewed*
- *Patients with GFR below 30 ml/min/1.73 m^2 have increased risk of developing NSF*
- *Low stability gadolinium contrast media show the strongest association with NSF*
- *Following guidelines regarding gadolinium contrast agents minimises the risk of NSF*
- *Potential long-term harm from gadolinium accumulation in the body is discussed*

Keywords Nephrogenic systemic fibrosis · Contrast media · Gadolinium · Renal insufficiency

Introduction

The Contrast Media Safety Committee of the European Society of Urogenital Radiology produced guidelines on nephrogenic systemic fibrosis (NSF) in 2007 [1]. Since then, more data have been published and different opinions have been presented. Therefore, the Committee decided to critically review the literature for new evidence and to update its guidelines for reducing the risk of NSF. The potential long-term problems from retention of small amounts of free gadolinium in the body after procedures enhanced with gadolinium-based contrast media are also considered.

Materials and methods

The literature was systematically reviewed by repeatedly checking the PubMed database for papers published from January 2001 to December 2011. The search term was "nephrogenic systemic fibrosis". In total, more than 656 papers were screened during the period of preparation of the review (Fig. 1). The type of study (randomised clinical trial, systematic review, meta-analysis) was not specifically used in the searches, but these terms were used when screening the abstracts. Cross-references were used when appropriate. Only manuscripts published in English were considered.

The strength of recommendation and the level of evidence of different prophylactic strategies for NSF were weighted and graded according to pre-defined scales (Tables 1 and 2). The same scales have previously been used by the Committee [2].

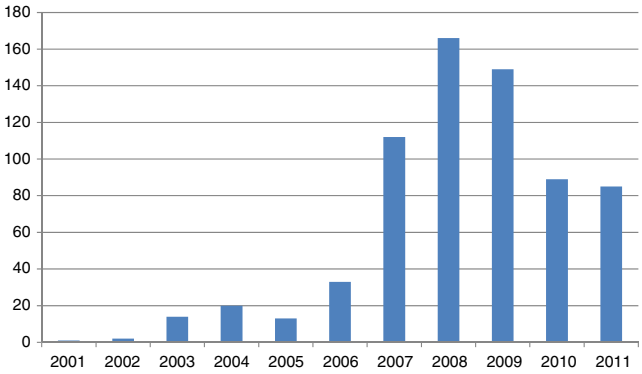

Fig. 1 Number of publications listed under "nephrogenic systemic fibrosis" in PubMed from 2001 to 2011. The decreasing number of papers probably reflects the fact that the incidence of NSF has been reduced to zero or almost zero after change to more stable agents

History of NSF

In 1996 the first article was published stating that, unlike iodine-based contrast media, gadolinium-based contrast media were not nephrotoxic [3]. This started the switch from iodine-based contrast media to gadolinium-based contrast media in patients with reduced renal function. Patients with reduced renal function were referred for enhanced magnetic resonance imaging (MRI) and gadolinium-based contrast media were also used for radiographic examinations such as computed tomography (CT) and conventional angiography [4]. Up to 440 ml of a gadolinium-based contrast medium were used for single angiographic examinations [5]. Multi-station MR angiography was introduced and patients received greater amounts of contrast medium for the whole examination, although the amount per station might not increase.

Not long after this, skin lesions which could not be identified as any recognised skin disease were seen in a few patients in California and subsequently similar lesions were diagnosed at three other universities. In 2000, Cowper published the first report about this new scleromyxoedema-like disease with fibrotic changes in the skin which occurred in renal dialysis patients [6].

In January 2006, Grobner [7] published a report suggesting a link between the development of similar skin lesions in five

Table 1 Level of evidence ratings

Level of evidence A	Data derived from multiple randomised clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomised clinical trial or large non-randomised studies.
Level of evidence C	Consensus of the opinion of experts and/or small studies, retrospective studies, registries.

Table 2 Classes of recommendation

CLASSES	DEFINITION
Class 1	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class 2	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class 2A	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class 2B	Usefulness/efficacy is less well established by evidence/opinion.
Class 3	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

out of nine patients with end-stage renal disease and exposure to gadodiamide during MR angiography. In August 2006, Marckmann et al. [8] reported a further 13 cases, again after exposure to gadodiamide in patients with end-stage renal disease. Several similar reports appeared in peer-reviewed journals in 2007 and 2008 [9–12]. The new condition was named nephrogenic systemic fibrosis (NSF), because it was associated with fibrotic changes in many organs, not just the skin.

Effects of gadolinium in the body

Gadolinium, a lanthanide, is used in magnetic resonance contrast media because it is paramagnetic and thus alters the relaxation properties of water protons during imaging, so producing changes in tissue contrast.

Free gadolinium is, however, highly toxic to the tissues [13–15]. The ionic radius of Gd^{3+} is close to that of Ca^{2+}, and gadolinium acts as an inorganic blocker of voltage-gated calcium channels [13]. Physiological processes dependent on Ca^{2+} influx (e.g. contraction of smooth, skeletal and cardiac muscle) and the activity of certain enzymes (e.g. some dehydrogenases and kinases) are therefore inhibited by Gd^{3+} [15, 16]. Also, calcium-sensing receptors on hepatocytes, renal cells, fibroblasts, etc. may be activated by gadolinium [16]. Gadolinium is a potent inhibitor of the reticuloendothelial system. Gadolinium chloride accumulates in the lysosomes of the Kupffer cells, inhibiting their phagocytic capacity and leading to their death [17]. The most pronounced acute toxic effects of free gadolinium occur in the liver, where it causes hepatocellular necrosis [18].

After administration, free gadolinium is sequestered in the liver and skeleton. Skeletal uptake is stable, whereas hepatic uptake is labile [13]. While there is no doubt that gadolinium accumulates in bone, it is still unclear whether gadolinium associates with the mineral content or the organic matrix of bone.

Gadolinium contrast media: types and stability

Because free gadolinium is toxic, it has to be administered to humans in a chelated form to avoid the presence of free gadolinium and so reduce toxicity. In the first commercially available gadolinium contrast medium, the chelating agent was diethylene triamine penta-acetic acid (DTPA), which had been used for many years combined with technetium (^{99m}Tc) for nuclear medicine studies. The resultant Gd-DTPA had high tolerance in animal studies, combined with good relaxation properties [19].

Current gadolinium contrast media have a variety of molecular structures: the molecules are linear or macrocyclic and can be ionic or non-ionic (Table 3) [20]. The molecular structure affects the stability of the molecules, i.e. how tightly the gadolinium is held within them.

In vitro measurements of the chemical stability of gadolinium contrast media show that the macrocyclic chelates are the most stable and that the non-ionic linear chelates are the least stable [21]. In the macrocyclic molecules the gadolinium is caged in the molecular ring, while in the linear molecules the gadolinium is held less strongly. Ionic linear molecules are generally more stable than non-ionic [21].

In vivo animal measurements support these findings, with three times more gadolinium retention in the tissues of rats and mice with normal renal function 2 weeks after the non-ionic linear agent gadodiamide than after the ionic linear agent gadopentetate dimeglumine. Only very small amounts of gadolinium were retained in the tissues after the macrocyclic agents gadobutrol, gadoterate meglumine and gadoteridol [22, 23].

Pathogenesis of NSF

The pathophysiology of NSF is not yet fully understood. However, a consistent body of knowledge from laboratory studies supports the idea that an important factor in the pathogenesis of NSF is the slow excretion of gadolinium-based contrast media in patients with severe renal impairment, allowing the lower stability gadolinium chelates to dissociate, releasing gadolinium.

The fibrogenic effects of the lanthanides, including gadolinium, were recognised as early as 1983 [24]. Lanthanides enhanced the polymerisation of skin collagen to a greater extent than calcium in studies in vitro and may be involved in the promotion of fibril formation [14, 25]. In the late

Table 3 The various commercially available gadolinium-based contrast agents and their characteristics [20]

Name	Brand name	Chelate/ ionicity	Viscosity mPa·s [c]	Osmolality mOsm/kg	Organ specific	Extracellular	Hepato-biliary excretion	T½[a]	Relaxivity in plasma 1.5 T – r_1 $mM^{-1}s^{-1}$ [c]	Relaxivity in plasma 3.0 T – r_1 $mM^{-1}s^{-1}$ [c]	Albumin binding	Stability	NSF risk[b]
Gadodiamide	Omniscan	Linear/non-ionic	1.4	780	No	Yes	No	1½ h	4.3	4.0	No	Low	High
Gadoversetamide	Optimark	Linear/non-ionic	2.0	1,110	No	Yes	No	1½ h	4.7	4.5	No	Low	High
Gadopentate dimeglumine	Magnevist	Linear/ionic	2.9	1,960	No	Yes	No	1½ h	3.9–4.1	3.7–3.9	No	Intermediate	High
Gadobenate dimeglumine	Multihance	Linear/ionic	5.3	1,970	Yes (liver)	Mainly	Yes (1%–4%)	1½ h	6.3–7.9	5.5–5.9	Yes (4%)	Intermediate	Intermediate
Gadoxetate disodium	Primovist, Eovist	Linear/ionic	1.2	688	Yes (liver)	No	Yes (42%–51%)	1½ h	6.9	6.2	Yes (10%)	Intermediate	Intermediate
Gadofosveset trisodium	Vasovist, Ablavar	Linear/ionic	2.1	825	Yes (blood)	No	Yes (5%)	18 h	19	9.9	Yes (90%)	Intermediate	Intermediate
Gadobutrol	Gadovist, Gadavist	Macrocyclic/ non-ionic	5.0	1,603	No	Yes	No	1½ h	4.7–5.2	4.5–5.0	No	High	Low
Gadoteridol	Prohance	Macrocyclic/ non-ionic	1.3	630	No	Yes	No	1½ h	4.1	3.7	No	High	Low
Gadoterate meglumine	Dotarem, Magnescope	Macrocyclic/ ionic	2.0	1,350	No	Yes	No	1½ h	3.6	3.5	No	High	Low

[a] In patients with normal renal function

[b] According to the EMA classification

[c] Determined at 37°C

1980s, rats which had received multiple injections of gadolinium contrast media over 3 weeks developed skin lesions after gadodiamide and gadopenamide, both non-ionic linear chelates, but not after the ionic agent gadopentetate dimeglumine [26, 27]. Gadodiamide was subsequently marketed, but gadopenamide was not.

Non-ionic linear gadolinium chelates can stimulate the proliferation of human fibroblasts, increase the accumulation of collagen in the extracellular matrix, and stimulate the production of pro-inflammatory and pro-fibrotic cytokines and growth factors from monocytes [28]. These effects seem to be gadolinium-dependent, since gadolinium chloride can induce similar stimulatory effects but the ligands of the gadolinium-based contrast agents do not [29].

Clinical features and diagnosis of NSF

NSF typically presents within 2 months of exposure to one of the less stable gadolinium-based contrast agents [30]. However, a few reports have highlighted possible late onset a few years after exposure [31].

Early symptoms and signs include skin discoloration, swelling and pain, with the lower extremities from the ankles to below the knees being predominantly affected in a symmetrical manner [30, 32]. The primary lesions are skin-coloured to erythematous papules, which coalesce into brawny lesions with a peau d'orange surface. After 6 months there are skin and subcutaneous sclerosis, induration, inflexibility, hair loss, shiny skin surface and brownish discoloration. The involved skin becomes markedly thickened with a woody texture. The skin thickening reduces joint movement, leading to flexion contractures of the limbs, with resultant significant disability. In some patients, severe disability necessitating assistance to move and use of a wheelchair has occurred within weeks after onset of symptoms. The lower limbs, thighs, forearms and hands may all be involved but the face is usually spared. The severity ranges from involvement of just a small patch of skin to extensive areas of the body being affected. NSF severity is graded from 0 to 4: 0=no symptoms, 1=mild physical, cosmetic or neuropathic symptoms not causing any kind of disability, 2=moderate physical and/or neuropathic symptoms limiting physical performance to some extent, 3=severe symptoms limiting daily physical activities (walking, bathing, shopping, etc.), 4=severely disabling symptoms causing dependence on aid or devices for common, daily activities [33].

The diagnosis of NSF is not easy and it is recommended that the clinical and pathological criteria for the diagnosis of NSF developed by the Yale NSF Registry are used to avoid misdiagnosis [34]. Careful clinical examination of the distribution and character of the lesions is essential. There are many other skin lesions in patients with reduced renal function which may closely resemble NSF, such as sclero-myxoedema, systemic sclerosis, morphea, lipodermatosclerosis and eosinophilic fasciitis. Deep skin biopsy must also be undertaken and carefully evaluated.

NSF is associated with increased mortality [35]. At post mortem, fibrotic changes may be seen in many tissues, including the muscles, lungs, liver and heart [30].

Treatment of NSF

There is currently no specific treatment for NSF. Some non-specific treatments, e.g. oral steroids and topical emollients, have been tried without consistent success [30].

Incidence

Data from the drug regulatory authorities and various registries (such as the Yale NSF Register) give an indication of the number of patients who have been diagnosed with NSF. For example, approximately 1,600 cases have been reported to the US Food and Drug Administration (FDA) [36]. Sixty hospitals in the United States account for 93% of these cases, and two hospitals in Denmark account for 4% of the cases. Determining the true prevalence of NSF is, however, difficult. Unless there is systematic examination of the skin in renal failure patients, particularly the lower extremities, cases are likely to be overlooked, especially if they are mild. However, only two reports have been published based on systematic inspection of the skin [35, 37]. It is likely that some patients may have died without having their NSF diagnosed [36] and that the prevalences reported are often underestimates. Conversely, reliance on skin examination only, without confirmatory biopsy, may over-diagnose NSF. For example, Todd et al. [35] reported that 30% of patients on dialysis, who had received a gadolinium-based contrast agent, had developed NSF, based on a systematic examination of the patients in five dialysis centres, but biopsies were only taken in a few patients.

The data available from several studies, based on dermatological, rheumatological, pathological or nephrology registers, suggest that the prevalence of NSF after exposure to gadodiamide is between 3% and 7% in patients with reduced renal function (CKD 4 & 5) [9].

Regulation

In May 2006 the FDA issued their first warning based on the reports from Austria and Denmark. In February 2007 the

European Medicines Agency (EMA) stated that the use of gadodiamide in patients with poor renal function was contra-indicated and in June 2007 the contra-indication was extended to gadopentetate dimeglumine. In July 2007 gadoversetamide was approved for the European market with the same contra-indication as had already been issued for gadodiamide and gadopentetate dimeglumine. In November 2008 Denmark requested a European review of gadolinium contrast media. In July 2010 the European Commission endorsed changes to the product summaries of the different gadolinium-based contrast agents proposed by the EMA; in general, the review confirmed the decisions taken by the EMA in 2007 [38]. In their reports, the EMA classify agents as being at high, intermediate or low risk of inducing NSF, based on their chemical properties. They recommend that intermediate risk agents are avoided in patients with poor renal function and that low risk agents can be used with caution. There are no clinical studies to support the differentiation of intermediate from low risk agents and the FDA does not make this distinction. In September 2010 the FDA finally followed the EMA and stated that gadoversetamide, gadodiamide and gadopentetate dimeglumine were contra-indicated in patients with poor renal function [39]. The marketing authorisation holder of gadoversetamide had already voluntarily stated that its use was contra-indicated in patients with poor renal function in November 2009. Since the fall of 2010 the drug regulatory authorities in Europe and the US have agreed about the precautions necessary for the use of gadolinium-based contrast agents [31].

Contrast medium-related NSF risk factors

1. Type of contrast agent

To be certain that a gadolinium-based contrast agent was a triggering factor for NSF, the case must be "unconfounded", i.e. the patient must not have received other gadolinium contrast media as well as the suspected triggering agent. Cases which have received more than one gadolinium-based contrast medium are described as "confounded".

In the peer-reviewed literature the majority of unconfounded cases of NSF, approximately 85%, were associated with gadodiamide, around 13% with gadopentate dimeglumine and a few cases with gadoversetamide [12, 30, 36]. Most of the reported series of ten patients or more involved gadodiamide and only one report documented more than ten patients following gadopentetate dimeglumine administration [9]. The higher prevalence of NSF with gadodiamide in comparison to gadopentetate dimeglumine is not a reflection of a higher market share, for gadopentetate dimeglumine has been given to up to four to five times the number of patients that have received gadodiamide.

The study by four American universities [40] showed an overall incidence of NSF after gadodiamide 13-times higher than after gadopentetate dimeglumine, with incidences of 0.039% and 0.003% respectively. The benchmark incidence of NSF was one in 2,913 patients who underwent gadodiamide-enhanced MRI and one in 44,224 patients who underwent gadopentetate dimeglumine enhanced MRI ($P<0.001$). This study used patient records from databases of dermatology, pathology, internal medicine, nephrology, transplant surgery and radiology departments, and patients with impaired renal function who had received gadolinium-based contrast media were not systematically examined [40].

It has also been reported that NSF has occurred after gadobutrol in a few patients who had not received another agent [41]. However, in these patients full pathological examinations were not performed; for example, in one patient CD34 stain was not used. It is unclear based on the manuscript whether the cases fulfil all the Yale clinical and histopathological criteria for NSF [34].

No proven unconfounded NSF cases fulfilling the Yale criteria have been linked with any of the gadolinium-based contrast media other than gadodiamide, gadoversetamide and gadopentetate dimeglumine.

2. Dose of contrast agent

Although NSF has been seen after a single dose (0.1 mmol/kg bodyweight) of gadodiamide [42] the risk of NSF seems to increase with increasing doses for single examinations and many reported cases occurred after multiple injections [30, 43]. In one study, 36% of patients developed NSF after two or more injections of gadodiamide compared with 12% after a single injection, indicating a cumulative effect [37]. Because records of contrast agent used and the dose given have often not been available, knowledge about possible cumulative effects after multiple injections is very limited.

Patient-related NSF risk factors

1. Impaired renal function

The National Institute for Health and Clinical Excellence uses five stages (Table 4) in their classification of chronic renal impairment [44]. The five-stage classification has been used in the majority of papers on NSF as well as by EMA [38].

Markedly reduced renal function is the most important patient-related risk factor for NSF and has been present in almost all reported cases of NSF, and many patients have been on haemodialysis or peritoneal dialysis. The degree of renal impairment appears to be important, with an incidence

Table 4 Stages of chronic kidney disease [44]

Stages	GFR (ml/min/1.73 m^2)	Description
1	≥ 90	Normal or increased GFR, with other evidence of kidney damage
2	60–89	Slight decrease in GFR, with other evidence of kidney damage
3A 3B	45–59 30–44	Moderate decrease in GFR, with or without other evidence of kidney damage
4	15–29	Severe decrease in GFR, with or without other evidence of kidney damage
5	< 15	Established renal failure including on dialysis

of histologically proven NSF of 18% following exposure to gadodiamide in patients with severe chronic kidney disease (CKD5, GFR less than 15 ml/min/1.73 m^2) [37] compared with the incidence of 3–7% in other series [9].

Renal function must always be measured shortly before the injection of the high risk gadolinium-based contrast agents to ensure that the patient does not have reduced renal function at the time of the examination. However, a single normal glomerular filtration rate (GFR) measurement does not rule out acute renal insufficiency, since there is a delay between a change in renal function and the corresponding change in serum creatinine. The patient's clinical condition should, therefore, also be assessed close to the time of the procedure and if factors which could cause acute renal failure are detected, the renal function should be measured again before the contrast medium is given. If there is a clinical suspicion of acute renal insufficiency, even if the patient has a GFR above 60 ml/min 1.73 m^2, a high-risk agent should not be administered, because the true GFR may be much lower.

Before low or intermediate risk gadolinium contrast agents are given, a questionnaire to identify patients with decreased renal function is considered adequate provided that there is a good clinical indication for an enhanced examination [45].

2. Liver failure

Some of the early reported cases of NSF were patients with severe liver dysfunction who were awaiting liver transplantation and who also had impaired renal function [46]. A recent review of over 2,000 patients who had undergone liver transplantation found that 709 patients had received gadolinium contrast media in the peri-transplant period. Of these, only one, who had CKD5 (GFR less than 15 ml/min/1.73 m^2) developed NSF. These findings suggest that there is no increased risk of NSF in patients with liver dysfunction but normal renal function [47].

3. Neonates

When NSF was first recognised, there was anxiety about the administration of gadolinium-based contrast media to neonates because neonatal renal function is immature. Thus, at age 1 week mean GFR is 40 ml/min/1.73 m^2, at 2–8 weeks mean GFR is 65 ml/min/1.73 m^2 and at 8 weeks, mean GFR is 95 ml/min/1.73 m^2 [48]. Although there have been no published reports of NSF in neonates, these theoretical considerations suggest that they may be at risk of NSF if they are given low stability gadolinium agents.

4. Other factors

When NSF was first recognised, it was suggested that there must be predisposing factors other than exposure to one of the less stable gadolinium-based contrast media, because not all patients with poor renal function who had received one of these agents developed NSF. Other possible factors which were suggested included inflammatory conditions, recent vascular surgery, use of high-dose erythropoietin (EPO), increased serum concentration of ionised calcium and phosphate, acidosis and the effect of iron (i.e. iron status and therapy) [30, 32]. Although no universal association with any of these factors has yet been shown, the possibility remains that one or more of these factors may have been significant in some patients.

Long-term effects of gadolinium in the body

Recently there have been reports of patients developing NSF years after exposure to gadolinium-based contrast agents [49, 50]. It is unclear where the gadolinium had been during the latent period, but it could have been sequestered in the bone. This could also explain the fact that the amount of gadolinium in the skin of NSF patients can increase for up to 3 years after exposure to a gadolinium-based contrast agent [51]. It has long been recognised that gadolinium can replace calcium in the hydroxyapatite of bone and that bone has a slow turnover. There is a concern that diseases, such as osteoporosis, which affect the bone turnover could cause the release of this retained gadolinium.

It has already been noted that, in mice and rats with normal renal function, gadolinium retention in the tissues 2 weeks after injection was three-times greater following the non-ionic linear agent gadodiamide than with the ionic linear chelate gadopentetate dimeglumine, while gadolinium retention in tissues was minimal with the macrocyclic agents [22]. Sieber et al. [52] also found that gadolinium accumulates in skin and bone of rodents with normal renal function. The amount of accumulated gadolinium was greater with

the lower stability agents. Wadas et al. [53] measured the uptake of ^{153}Gd-based contrast media in mice with normal and impaired renal function. After 7 days, mice with renal impairment that had received the ionic macrocyclic chelate had three-times more radioactivity in their bone tissue than control mice. However, mice with renal impairment that had received an ionic linear chelate or a non-ionic linear chelate had eight-times and 24-times more radioactivity in their bone tissue, respectively. White et al. [54] found four-times more gadolinium in the bones of patients with normal renal function after a non-ionic linear chelate than after a non-ionic macrocyclic chelate, but the time from injection to removal of the bone varied in the two groups.

The European Commission has decided that the marketing authorisation holders should submit protocols and timelines for studies evaluating the potential for long-term accumulation of gadolinium in human bone to the EMA [38]. It is recommended that bone samples are obtained from patients undergoing hip and knee replacement surgery. Co-factors that may increase the risk of NSF, such as calcium and phosphate levels at the time of administration of gadolinium-based contrast media, should be studied and biomarkers evaluated. It will take a number of years before the results of this important study are available.

Pregnancy and lactation

The recent appreciation of the possibility of retention of small amounts of gadolinium contrast media in the body for long periods, with the possibility of the release of free gadolinium has necessitated a re-evaluation of the use of gadolinium-based contrast media in pregnant and lactating patients [55].

The new data has led to more stringent ESUR CMSC recommendations for the use of gadolinium-based contrast media aimed at protecting the fetus from long-term harm. The recommendations state that gadolinium-based contrast media should only be given to pregnant women when there is a very strong clinical indication. One of the low or intermediate risk agents should be used in the lowest dose to achieve a diagnostic result.

Similarly, although only small amounts of gadolinium-based contrast media are excreted into human breast milk [55], the immaturity of the fetal kidneys could delay their excretion with the possibility of long-term accumulation of gadolinium in the tissues. The ESUR CMSC recommends that if lactating patients receive one of the high risk agents, they should stop breast feeding for 24 h and discard the milk. For the other gadolinium-based contrast agents, the decision about whether to stop breast feeding should be made by the mother in consultation with her medical advisor.

Haemodialysis

Haemodialysis has been recommended for renal failure patients on dialysis immediately after they have received gadolinium-based contrast agents [30, 56]. However, no evidence that haemodialysis protects against NSF has been published. It has been estimated that three consecutive haemodialysis treatments over a 6-day period would be needed to remove 97% of the administered extracellular gadolinium-based contrast agent [57].

Guidelines: levels of evidence and recommendation

Based on the evidence presented in this review, the ESUR CMSC's new guidelines (Table 5) are summarised below, with their strength of evidence and recommendation ratings (Tables 1 and 2)

1. Contrast agents with highest risk of NSF (Gadodiamide, Gadopentetate dimeglumine and Gadoversetamide):
   (a) Contra-indicated in CKD4 and 5 (GFR less than 30 ml/min/1.73 m^2), patients on dialysis and patients with acute renal insufficiency. *Level of evidence B, Class of recommendation 1.*
   (b) Contra-indicated in neonates and pregnant women. *Level of evidence C, Class of recommendation 2B.*
   (c) Should be used with caution in patients with CKD 3 (GFR 30–60 ml/min/1.73 m^2) with at least 7 days between injections. *Level of evidence C, Class of recommendation 2A.*
   (d) Should be used with caution in children less than I year. *Level of evidence C, Class of recommendation 2B.*
   (e) Lactating women should not breastfeed for 24 h after contrast medium and should discard the breast milk. *Level of evidence C, Class of recommendation 2B.*
   (f) Serum creatinine (eGFR) and clinical assessment of the patient are mandatory before contrast medium administration. *Level of evidence A, Class of recommendation 1*
   (g) Should never be given in doses greater than 0.1 mmol/kg in any patient. *Level of evidence B, Class of recommendation 1*
2. Contrast agents with intermediate risk of NSF (Gadobenate dimeglumine, Gadofosvest trisodium, Gadoxetate disodium) and contrast agents with lowest risk of NSF (Gadobutrol, Gadoterate meglumine and Gadoteridol)
   (a) Should be used with caution in patients with CKD4 and 5 (GFR less than 30 ml/min/1.73 m^2) including patients on dialysis, with at least 7 days

Table 5 Updated ESUR guidelines on gadolinium-based contrast agents and NSF

Nephrogenic systemic fibrosis	
A diagnosis of nephrogenic systemic fibrosis (NSF) should only be made if the Yale NSF Registry clinical and histopathological criteria are met (J Am Acad Dermatol 2011; 65:1095–1106). The link between nephrogenic systemic fibrosis (NSF) and gadolinium-based contrast agents was recognised in 2006.	
Clinical features of NSF	*Onset:* From the day of exposure for up to 2–3 months, sometimes up to years after exposure. 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
Patients	
At higher risk	• Patients with CKD 4 and 5 (GFR<30 ml/min) • Patients on dialysis • Patients with acute kidney insufficiency
At lower risk	• Patients with CKD 3 (GFR 30–59 ml/min)
Not at risk of NSF	• Patients with stable GFR>60 ml/min)
Contrast agents: Risk Classification (based on laboratory data) and Recommendations	
Highest risk of NSF	
• Contrast agents	Gadodiamide (Omniscan®) *Ligand*: Non-ionic linear chelate (DTPA-BMA) *Incidence of NSF*: 3–18% in at-risk subjects Gadopentetate dimeglumine (Magnevist® plus generic products) *Ligand*: Ionic linear chelate (DTPA) *Incidence of NSF*: Estimated to be 0.1–1% in at risk subjects Gadoversetamide (Optimark®) *Ligand*: Non-ionic linear chelate (DTPA-BMEA) *Incidence of NSF*: Unknown.
• Recommendations	These agents are CONTRA-INDICATED in • patients with CKD 4 and 5 (GFR<30 ml/min), including those on dialysis • acute renal insufficiency • pregnant women • neonates These agents should be used with CAUTION in • patients with CKD 3 (GFR 30–60 ml/min) ○ There should be at least 7 days between two injections • children less than 1 year old Lactating women: Stop breastfeeding for 24 h and discard the milk. Serum creatinine (eGFR) measurement and clinical assessment of patient before administration: *Mandatory* These agents should never be given in higher doses than 0.1 mmol/kg per examination in any patient
Intermediate risk of NSF	
• Contrast agents	Gadobenate dimeglumine (Multihance®) *Ligand*: Ionic linear chelate (BOPTA) *Incidence of NSF*: No unconfounded[a] cases have been reported. *Special feature:* It is a combined extracellular and liver specific agent with 2–3% albumin binding. Diagnostic results can be achieved with 50% lower doses than with usual extracellular agents. In man □4% is excreted via the liver. Gadofosveset trisodium (Vasovist®, Ablavar®) *Ligand*: Ionic linear chelate (DTPA-DPCP) *Incidence of NSF*: No unconfounded[a] cases reported, but experience is limited *Special feature*: It is a blood pool agent with affinity to albumin (> 90%). 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 with 1½ h, respectively); 5% is excreted via the bile. Gadoxetate disodium (Primovist®, Eovist®) *Ligand*: Ionic linear chelate *(EOB-DTPA)* *Incidence of NSF*: No unconfounded[a] cases have been reported but experience is limited. *Special feature*: It is an 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.
• Recommendations	These agents should be used with CAUTION in • patients with CKD 4 and 5 (GFR <30 ml/min) ○ There should be at least 7 days between two injections Pregnant women: Can be used to give essential diagnostic information.

Table 5 (continued)

	Lactating women: The patient should discuss with the doctor whether the breast milk should be discarded in the 24 h after contrast medium.
	Laboratory testing of renal function (eGFR) is *not mandatory.*
	Renal function assessment by questionnaire should be used if serum creatinine is not measured.
Lowest risk of NSF	
• Contrast agents	Gadobutrol (Gadovist®, Gadavist®)
	Ligand: Non-ionic cyclic chelate (BT-DO3A)
	Incidence of NSF: A few unconfounded[a] cases have been reported, but there is uncertainty about the histopathological changes.
	Gadoterate meglumine (Dotarem®, Magnescope®)
	Ligand: Ionic cyclic chelate (DOTA)
	Incidence of NSF: No unconfounded[a] cases have been reported.
	Gadoteridol (Prohance®)
	Ligand: Non-ionic cyclic chelate (HP-DO3A)
	Incidence of NSF: No unconfounded[a] cases have been reported.
• Recommendations	These agents should be used with CAUTION in
	• patients with CKD 4 and 5 (GFR <30 ml/min)
	○ There should be at least 7 days between two injections
	Pregnant women: Can be used to give essential diagnostic information
	Lactating women: The patient should discuss with the doctor whether the breast milk should be discarded in the 24 h after contrast medium.
	Laboratory testing of renal function (eGFR) is *not mandatory.*
	Renal function assessment by questionnaire should be used if serum creatinine is not measured.
Patients with NSF	Gadolinium-based contrast media should only be used if the indication is vital and then only intermediate or low risk agents should be used.
Recommendation for all patients	Never deny a patient a clinically well-indicated enhanced MRI examination.
	In all patients use the smallest amount of contrast medium necessary for a diagnostic result.
	Always record the name and dose of the contrast agent used in the patient records.

[a] *Confounded cases:* If two different Gd-CM have been injected, it is impossible to determine with certainty which agent triggered the development of NSF and the situation is described as "confounded"

Unconfounded cases: The patient has never been exposed to more than one agent.

between 2 injections. *Level of evidence C, Class of recommendation 2B*.

(b) Can be used in pregnant women to give essential diagnostic information. *Level of evidence C, Class of recommendation 2B.*

(c) In lactating women the decision about whether to stop breast feeding and discard the breast milk for 24 h after contrast medium should be made by the woman after discussion with the doctor. *Level of evidence C, Class of recommendation 2B.*

(d) Serum creatinine (eGFR) measurement before administration is not mandatory. Renal function assessment by questionnaire is sufficient. *Level of evidence C, Class of recommendation 3.*

Conclusion

Since the ESUR CMSC guidelines on NSF were published in 2007 [1], a considerable body of clinical and experimental data has been published. Despite this, the new guidelines only contain minor revision of the 2007 recommendations. The key features of the guidelines remain the need to identify patients with impaired renal function and the restrictions placed on giving such patients gadolinium-based contrast media, which are most stringent with the lowest stability (highest risk) agents. Following the warnings from the FDA and EMA in 2007, and publication of the ESUR CMSC and American College of Radiology guidelines, the number of new cases of NSF being reported has decreased dramatically.

Since NSF was recognised, reviews of the stability of the gadolinium-based contrast media and of data both from the early 1990s [22, 26] and more recently [52–54] have led to anxieties about the possible long-term effects of free gadolinium in the tissues, including the bone. These concerns led to the recommendations in the guidelines for pregnant and lactating women with the aim of protecting the fetus or breast-fed infant when a gadolinium-based contrast agent is given to the mother. Another concern is the possible long-term effect of gadolinium in the bone, even in patients with normal renal function, and especially those who have received low-stability agents. Are such patients at risk of release of free gadolinium if their bone turnover increases or if they subsequently receive more gadolinium-based contrast medium, even if a macrocyclic agent is used? The European study collecting information about gadolinium deposition in bone removed during joint surgery [38] is likely to be helpful. Investigation of possible co-factors, such as the calcium and phosphate levels when gadolinium-based contrast media were given, should be undertaken. There is still concern that NSF is only the "tip of the gadolinium toxicity iceberg" [58].

An unfortunate result of anxieties about NSF has been that enhancement during MRI may be avoided inappropriately and important disease overlooked. In a patient with mild or moderate renal impairment, the risk of NSF from an MR examination enhanced with one of the most stable gadolinium-based agents is likely to be less than the risk of nephrotoxicity from a CT examination enhanced with an iodine-based agent [59, 60].

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