

Guidance on gadolinium-based contrast agent administration to adult patients

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Foreword

The first human use of gadolinium chelated with diethylenetriamine penta-acetic acid (DTPA) as a contrast agent for magnetic resonance imaging (MRI) was in 1983.¹ Since then there has been a huge increase in the use of gadolinium-based contrast agents (GBCAs) with well documented safety. Nevertheless, concerns have been raised in relation to nephrotoxicity, the development of the very rare condition of nephrogenic systemic fibrosis (NSF) and the potential impact of long-term gadolinium retention, particularly in the brain.

Precautionary measures instigated in 2006 to mitigate against the risk of NSF by restricting the use of linear chelate GBCAs in patients with impaired renal function and using lower doses of macrocyclic chelate GBCAs to achieve diagnostic-quality studies have resulted in no new cases of NSF in Europe in patients administered GBCAs since that time.

The more recent publications investigating the potential for long-term gadolinium retention in the brain and other organs have resulted in recommendations that marketing authorisations for some linear chelate GBCAs were withdrawn and others amended. The RCR published a statement highlighting the licensing changes.²

These important issues are discussed in depth and huge thanks go to Dr Giles Roditi for drafting this guidance and providing expert advice to the Medicines and Healthcare products Regulatory Agency (MHRA).

This guidance replaces the previous guidance on *Gadolinium-based contrast media and nephrogenic systemic fibrosis* and *Standards for intravascular contrast administration in adult patients, third edition*, which have now been archived. The RCR endorses The Royal Australian and New Zealand College of Radiologists' 2016 Iodinated Contrast Guidelines, which can be viewed at online.³

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1. Recommendations

The key recommendations outlined in this guidance are as follows.

1. An individual trained in recognising and treating severe contrast reactions, including anaphylaxis, should be immediately available for the department where intravenous contrast is administered.
2. A formal record of the decision to inject contrast should be made before administration.
3. The individual administering the contrast must check that there are no contraindications to its use and ensure that the patient understands that it is to be given and agrees to the procedure.
4. In cases where there is a previously reported moderately severe or severe reaction to contrast, caution should be exercised and the need for the use of contrast should be re-examined with respect to an unenhanced study or other potential methods of investigation.
5. For elective examinations in patients who have a history of previous contrast reaction, consideration should be given to referral to a specialist drug allergy service for assessment and testing against a panel of contrast compounds to determine the safety of administration.
6. The dose of GBCA should be minimised, taking into consideration the indication, the patient's body weight and the information from the manufacturer contained in the summary of product characteristics. The dose administered should be recorded electronically for audit purposes.
7. When using GBCAs, knowledge of the patient's renal functional status is generally advisable. GBCAs should be used with caution in patients with severe chronic or acute renal impairment, patients in the perioperative liver transplantation period and in neonates.
8. Significant suspected contrast reactions should be formally documented with full details, investigated appropriately with advice given to the patient and referral made to a specialist drug allergy service to help guide future management.

2. Introduction

The first human use of gadolinium chelated with DTPA as a contrast agent for MRI was in 1983, this compound later becoming commercially available for clinical use in 1988.¹ GBCAs work through the paramagnetic properties of the gadolinium ion with seven unpaired electrons changing the local magnetic field. Free gadolinium ions are highly toxic; hence they are made safe for clinical use by binding to a ligand – that is, formulation as a chelated compound. Gadolinium ions are similar in size and capable of binding to many of the same sites as calcium. The chelate binds the gadolinium ion tightly allowing excretion of the intact complex. Although there is theoretical potential for dissociation of gadolinium from the chelate, the compounds are designed to absolutely minimise this.

There has been a huge increase in the use of GBCAs in radiology since their commercial introduction. Indeed, worldwide there are currently more than 30 million patient administrations per year, perhaps one-in-three of all MRI studies.⁴ In the main this is due to their clinical utility balanced against their excellent safety record. While GBCAs are potentially nephrotoxic similar to iodine-based contrast media in equimolar quantities, the clinically approved small amounts used means that this is not generally a clinical issue.⁵ However, in 2006 the association between the administration of GBCAs in patients with severe renal failure and development of the very rare condition nephrogenic systemic

fibrosis (NSF) came to light prompting a review of the different agents which in Europe were subsequently classified by the European Medicines Agency on the perceived risk of dissociation.^{6,7} Subsequently, restrictions were imposed on the use of linear chelate GBCAs in patients with impaired renal function while the macrocyclic chelate GBCAs (with the lowest potential for dechelation) were less constrained.

Widespread use of GBCAs continued, including of those most frequently associated with NSF. Yet because of the response of the radiology community, avoiding the less stable linear chelate 'high-risk' GBCAs in those patients known to be at greatest risk for NSF, no new cases related to exposure to the agents following the restrictions have been reported in Europe.⁸ There have been reported cases of NSF manifesting subsequent to the changes, albeit associated with the administration of 'high-risk' GBCAs to patients with severe renal failure prior to the Food and Drug Association (FDA) warning of 2007, essentially late presentations although the reasons for these delayed manifestations are obscure.⁹

More recently the general issue of gadolinium retention has come to the fore, spurring much research. Subsequently the decision in Europe has been to implement further restrictions to linear chelate GBCA use. This followed a series of publications investigating signal hyperintensity on unenhanced T1 weighted MRI of the brain (involving the dentate nucleus and basal ganglia) in patients that have previously been administered multiple doses of GBCAs which indicate that there may be long-term gadolinium retention in the brain.^{10,11} This brain retention, albeit in tiny amounts, has been subsequently confirmed on cadaver studies.^{12,13}

Data from both animal and human studies have previously demonstrated that gadolinium can accumulate in very low concentrations in a range of tissues and organs (skin, bone, liver, kidney, muscle and spleen). Retention in the brain is in even lower concentrations than other parts of the body and has been shown to be much lower for the macrocyclic agents than the linear agents.^{14,15} However, the exact state of this gadolinium in terms of whether it has been dechelated and bound now to another compound or still as the intact original GBCA is not clear. Although it appears that dechelation has occurred at least to some extent in the brain with the less stable linear chelates this has not been shown with any of the macrocyclic GBCAs.¹⁶ The clinical consequences, if any, of this retention are unknown but studies to date have been reassuring.¹⁷

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) commenced an investigation in March 2016 stimulated by the work published since 2014 and the subsequent concerns regarding gadolinium retention following administration of GBCAs. Following this investigation and a consultation process the PRAC submitted recommendations in 2017 to the Committee for Medicinal Products for Human Use (CHMP) on revisions to the marketing authorisations for the available GBCAs. Although there is currently no evidence that gadolinium retention in the brain has caused adverse neurological effects to patients, the recommendations have now been accepted by the CHMP as a precautionary measure. As a result, the marketing authorisations of some linear chelate GBCAs were withdrawn while others were amended. The following is a summary of the changes as they apply to the different agents in Europe.

1. **Gadopentetate dimeglumine (Magnevist, Bayer + generic products such as MagneGita, Agfa), Gadodiamide (Omniscan, GE Healthcare) and Gadoversetamide (OptiMARK, Guerbet – previously Mallinckrodt)** – these agents

had their marketing authorisations for intravenous administration suspended in Europe as a precautionary measure and should no longer be used.

2. **Gadobenate dimeglumine (MultiHance, Bracco) and Gadoxetic acid (Primovist, Bayer)** – these agents will remain on the market with their indication limited to liver imaging only, and when imaging in the delayed phase is required. This would include protocols where dynamic imaging involving acquisition of arterial phases is combined with delayed phase scans. MultiHance previously had a ‘whole-body’ license. Departments that have been using this agent for indications other than liver imaging (which can continue) should make arrangements to switch to those agents with continued authorisation for more general work (see below). Where MultiHance has been used purposefully for its higher specific relaxivity (for example in central nervous system [CNS], breast and vascular imaging) then radiologists will have to determine what dose of the alternative agents will need to be used to obtain equivalent enhancement for their protocols, bearing in mind that this should be at the lowest dose that is effective for diagnosis. This will require changes to the local standard operating procedures (SOPs) and associated patient group directions (PGDs) under which MRI contrast agents are administered.^{18,19}
3. **Gadopentetate dimeglumine 2 mmol/l solution for intra-articular injection (Magnevist, Bayer)** – this low-dose, dilute solution of Magnevist specifically formulated for intra-articular injection during MRI arthrography remains on the market with no change to its marketing authorisation.
4. **Gadoteric acid (Dotarem, Guerbet and Clariscan, GE Healthcare), Gadoteridol (ProHance, Bracco) and Gadobutrol (Gadovist, Bayer)** – these agents all remain on the market with updated advice to emphasise that GBCAs should only be used when essential diagnostic information cannot be obtained with unenhanced scans and using the lowest dose effective for diagnosis. The RCR recommends that the local SOPs and associated PGDs be reviewed with this advice in mind.

The potential and theoretical risks of intravenous administration of GBCAs for MRI must be weighed against the potential benefits to the patient. (It should be noted that GBCAs are not approved for intra-arterial injections or enhancement of radiographic examinations such as invasive arteriography.) Withholding contrast for MRI may deprive patients of the benefits of valuable diagnostic information or necessary therapy. This document aims to provide guidance on how GBCAs may be used as safely as possible with adult patients. For children and neonates, a paediatric radiologist should be consulted.

3. General safety issues

GBCAs are associated with a very low rate of immediate adverse events (0.06%–0.09%).^{20,21}

Most adverse events are mild and can be managed in the radiology department.

Major life-threatening contrast reactions to GBCAs are extremely rare. The incidence of acute, severe reactions is estimated to be 0.0025–0.005%.^{20,21}

To minimise risk, it is important to identify individuals at an increased risk of an adverse event.

Appropriate steps should always be taken to reduce the risk of contrast reactions.

4. Practical safety issues

An individual trained in recognising and treating severe contrast reactions, including anaphylaxis, should be immediately available for the department. This could be a registered nurse or radiographer or other appropriately trained healthcare professional.

There should be systems in place to call an appropriately trained doctor who can deal immediately with a severe contrast reaction. If required, this may include a crash team.

In the presence of risk factors, the decision about contrast administration should only be taken by the radiologist responsible for the procedure. This decision process should include the location of the proposed examination with reference to resuscitation capability.

Facilities for the treatment of acute adverse reactions should be readily available and regularly checked within the department.

A patient should not be left alone or unsupervised in the first five minutes after an injection of any intravascular contrast.

It is advisable that the patient remains on the premises for at least 15 minutes following the injection. Most severe reactions occur during this time. For patients identified as at increased risk of a reaction, this should be increased to 30 minutes following the injection.

All contrast reactions, with details of their nature, severity and the specific compound used, should be included in the radiological report, updated in the patient's hospital notes and on the radiology information system (RIS).

5. Prescribing contrast

A formal record of the decision to inject intravascular contrast should be made before administration.

How this is achieved will depend on local circumstances, but may include:

- Setting up a patient group direction to cover specific scan protocols
- A formal written record by the radiologist, signed and dated on the request and either filed in the radiology department or scanned into the RIS
- Recording the decision electronically, directly into the RIS as part of the vetting and protocol assignment process
- A formal prescription on the patient's drug chart.

6. Patient information and consent

The patient should always be fully informed about any procedure and understand what it will involve.

Appropriate patient information leaflets should be available in the department. The individual administering the contrast must check that there are no contraindications to its administration and ensure that the patient understands that it is to be given and agrees to proceed.

7. Identifying patients at increased risk from contrast administration

The ultimate responsibility for contrast administration rests with the person who prescribes it, although delivery of the injection is frequently delegated to others under local rules and protocols.

Essential information which should be sought from the patient before a contrast injection includes history of:

- Previous contrast reaction
- Renal problems.

Ideally, this information will be available when the examination is requested but should always be checked in the department before injection.

8. Recommendations for contrast use in patients at increased risk

History of previous contrast reaction

Caution should be exercised when there is a previously reported moderately severe reaction (such as bronchospasm or urticaria requiring treatment) or severe reaction (for example, laryngeal or angioneurotic oedema, severe bronchospasm or collapse) to intravascular contrast.²²⁻²⁴

The prescriber should:

- Determine the exact nature of the previous reaction
- Identify the specific compound used on that occasion
- Re-examine the need for the use of contrast, with respect to an unenhanced study or other potential methods of investigation
- Where a decision has been made to proceed with contrast administration in a patient at increased risk, following the study, leave the cannula in place and keep the patient under observation for 30 minutes after the injection
- Be ready to treat any adverse reaction promptly and ensure that emergency drugs and equipment are available.

Asthma, multiple allergies or a documented severe allergy requiring therapy

Individuals with asthma, multiple well-documented allergies or a single very severe allergy are at an increased risk.²²⁻²⁴

The prescriber should determine:

- Whether the patient has true asthma or chronic obstructive pulmonary disease (COPD)
- Whether the asthma is currently well controlled.

If the patient is wheezy or reports that their asthma is currently not well controlled and the examination is not urgent, it should be deferred and the patient referred back for appropriate medical therapy.

If the asthma is well controlled, reassess the need for intravascular contrast with respect to an unenhanced study or other potential methods of investigation.

For patients with multiple or severe allergies, determine their nature and re-examine the need for contrast administration with respect to an unenhanced study or other potential methods of investigation. For elective examinations, consult with a specialist drug

allergy service for testing the patient against a panel of GBCAs to determine safety of administration.²⁴

Renal disease, diabetes mellitus and conditions associated with renal impairment

High volumes of GBCAs are nephrotoxic and in the presence of renal impairment there is potential for contrast-induced acute kidney injury (CI-AKI).

Advice

Large volumes of GBCAs (>30 millilitres [ml]) should not be used. GBCAs should only be used for enhancement in MRI scans and not for opacification in X-ray based procedures such as invasive arteriography or computed tomography (CT) for which they are not approved. Previous terminology such as contrast nephrotoxicity, contrast-induced nephropathy (CIN) or radiocontrast nephropathy (RCN) have been replaced by post-contrast acute kidney injury (PC-AKI), in line with other causes of acute kidney injury.^{10,11} (See Appendix 1 for a definition of PC-AKI).^{5,25-27}

There is no need to stop metformin after GBCA administration.

9. Pregnancy and lactation

Pregnancy

There is little human data regarding the use of GBCAs in pregnant women.²⁸ While animal data and the limited observational human literature are reassuring as regards any potential effects to reproductive toxicity, GBCAs should not be used during pregnancy unless the clinical condition of the patient makes their use absolutely necessary. No effect on the developing fetus is anticipated.

Lactation

A very small percentage of the injected dose of GBCA enters the breast milk and virtually none is absorbed across the normal gut. While no special precaution or cessation of breastfeeding is required the continuation or cessation of breast feeding for 24 hours should be at the discretion of the lactating mother in consultation with the clinician.

10. Nephrogenic systemic fibrosis

GBCAs are remarkably safe, with a lower adverse event rate for both allergic type reactions and nephrotoxicity than iodine-based contrast media. However, the administration of high doses of the non-specific linear chelate agents in patients with severe renal failure has, in the past, been associated with the development of the very rare condition nephrogenic systemic fibrosis (NSF). See advice below to minimise this risk from GBCAs in the following vulnerable groups:

- Patients with renal impairment
 - Patients in the perioperative liver transplantation period
 - Infants, neonates and the elderly
 - Women who are pregnant or breastfeeding.
-

NSF is an extremely rare but serious and potentially life-threatening condition characterised by the deposition of collagen in the skin which becomes thickened, coarse and hard, sometimes leading to contractures and joint immobility. Patients with NSF can have systemic involvement of other organs, including the lungs, liver, muscles and heart. The cause of NSF is not fully understood but the consensus is that it is associated with the administration of linear chelate gadolinium contrast agents in patients with severe renal impairment. A diagnosis of NSF is based on a combination of clinical and pathological criteria (see Appendix 3).²⁹ While in most instances of NSF, the onset of symptoms can be identified to be from the day of exposure to two or three months later, it is now recognised that clinical manifestations may present years later, the reasons for and mechanisms underlying this are not understood currently.^{9,30}

Some GBCAs have been much more associated with the development of NSF than others. In 2017 the CHMP of the European Medicines Agency (EMA) suspended the linear chelates thought to be highest risk from intravascular use.

The EMA's Scientific Advisory Group on Diagnostics had previously concluded that the cyclic products (those with the lowest risk) can be used for patients with severely reduced renal function when a contrast-enhanced MRI scan is clearly the best method of examination.

The committee did not recommend contraindicating the use of these GBCAs in patients with renal impairment because, in some cases, there are no alternatives, although dose should be limited to the minimum consistent with the investigation being carried out. This classification has not been revised since initial publication but remains appropriate as research continues to reinforce the association of cases of NSF with the use of those linear chelates previously classified as high-risk and now suspended.

Advice

The following risk minimisation measures should be used for GBCAs. This advice is adapted from the current Medicines and Healthcare products Regulatory Agency (MHRA) advice.³¹

Renal function monitoring

Renal function testing is generally advisable and is particularly important to screen patients aged 65 years or older and patients with chronic diseases, such as diabetes, which are associated with renal failure.

Renal impairment

For patients with severe chronic renal impairment (eGFR <30 ml/minute/1.73 m²) or acute renal impairment if, after clinical review, use of a low-risk agent is appropriate or if it is necessary to use a medium-risk agent (such as for liver imaging), a single lowest dose possible can be used (a dose not exceeding 0.1 millimoles [mmol]/kilogram [kg] body weight) and should not be repeated for at least seven days.

Avoid administering GBCAs in acute kidney injury while creatinine is rising.

For patients with moderate chronic renal impairment (eGFR 30–59 ml/min/1.73 m²) if, after clinical review, it is necessary to use a contrast agent, a single lowest dose possible should be used and should not be repeated for at least seven days.

Perioperative liver transplantation period

If the use of a low-risk macrocyclic agent is required (or if it is necessary to use a medium-risk agent specifically for liver imaging) a single lowest dose possible can be used and should not be repeated for at least seven days.

Haemodialysis

There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis, as emergency initiation of dialysis entails significant risks. However, those patients already established on dialysis should be dialysed promptly after contrast administration (certainly within 24 hours).³²

Recording of the agent used

When they are available, 'peel-off' tracking labels found on the vials, syringes or bottles should be stuck onto or scanned into the patient record to maintain an accurate note of the name and batch of the gadolinium contrast agent used.

The dose used should also be documented.

Suspected adverse reactions should be reported on a Yellow Card to the MHRA.³³

11. Treatment of acute reactions

Simple guidelines for the treatment of acute reactions are presented below.

Nausea/vomiting

- Transient: supportive treatment.
- Severe, protracted: appropriate anti-emetic drugs should be considered.

Urticaria

- Scattered, transient: supportive treatment, including observation.
- Scattered, protracted: appropriate H1-antihistamine orally or intramuscularly should be considered. Drowsiness and/or hypotension may occur.
- Profound: consider adrenaline 1:1000, 0.1–0.3 ml (0.1–0.3 milligrams [mg]) intramuscularly. Repeat, as needed.

Bronchospasm

- Oxygen by mask (6–10 litres [l]/min).
- β 2-agonist metered dose inhaler (2–3 deep inhalations).
- Adrenaline:
 - Elevate patient's legs
 - Normal blood pressure: adrenaline 1:1000, 0.1–0.3 ml (0.1–0.3 mg) intramuscularly. Use smaller dose in a patient with coronary artery disease or elderly patient
 - Decreased blood pressure: adrenaline 1:1000, 0.5 ml (0.5 mg) intramuscularly.

Laryngeal oedema

- Oxygen by mask (6–10 l/min).
 - Adrenaline 1:1000, 0.5 ml (0.5 mg) intramuscularly. Repeat as needed.
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Hypotension

- Isolated hypotension.
 - Oxygen by mask (6–10 l/min)
 - Intravenous fluid: rapidly, normal saline or lactated Ringer's solution
 - If unresponsive: adrenaline 1:1,000, 0.5 ml (0.5 mg) intramuscularly. Repeat as needed.
- Vagal reaction (hypotension and bradycardia).
 - Elevate patient's legs
 - Oxygen by mask (6–10 l/min)
 - Atropine 0.6–1.0 mg intravenously, repeat if necessary. After 3–5 min, to 3 mg total (0.04 mg/kg)
 - Intravenous fluids: rapidly, normal saline or lactated Ringer's solution.

Generalised anaphylactic reaction

- Call for resuscitation team.
- Suction airway if needed.
- Elevate patient's legs if hypotensive.
- Oxygen by mask (6–10 l/min).
- Adrenaline: 1:1000, 0.5 ml (0.5 mg) intramuscularly.
- H1 blocker, for example, chlorpheniramine 10–20 mg intravenously.

Recording and investigation of significant suspected contrast reactions

- For anaphylaxis (severe multisystem reaction) or for severe urticaria or angioedema without systemic features, record details of the incident with a description in the report and notes, including generic and proprietary names of the contrast used plus batch number.
- For anaphylaxis, take blood samples for mast cell tryptase in line with recommendations in *Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode*.³⁴
- Discuss the patient's suspected contrast reaction with them and their carers, if appropriate, and provide written information.
- Arrange referral to a specialist drug allergy service to help guide future management.
- Suspected adverse reactions should be reported on a Yellow Card to the MHRA.³³

Contrast agent extravasation

- Record details of the incident with management advice in the report and notes.
- Elevate the affected limb.
- If symptoms resolve such that an outpatient can be allowed home, supply the patient with an appropriate advice leaflet.
- If symptoms do not resolve quickly, admit and monitor.
- Skin blistering, paraesthesiae, altered tissue perfusion and increasing or persistent pain for more than four hours suggest severe injury. In this case, seek surgical advice (plastic surgeon).^{35–37}

12. Conclusions

The use of GBCAs has become fundamental to MRI and the compounds used in daily practice are extremely safe. However, as our knowledge expands regarding the potential to prevent and risk manage adverse events associated with the use of intravascular contrast, so it is appropriate that guidance is revised and standards are set for safe administration. This most recent revision to the RCR guidance builds upon earlier work.

The intention of this document is to clarify those factors that should be taken into account for the prevention and treatment of adverse events related to the use of intravascular GBCAs. Compliance with the proposed guidance in this document should translate directly into high-quality care for the many patients referred to departments of radiology for diagnostic imaging and image-guided intervention.

This document was approved by the Clinical Radiology Professional Support and Standards Board on 7 February 2019.

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Appendix 1. Post-contrast acute kidney injury

Post-contrast acute kidney injury (PC-AKI) is a general term used if there is a sudden deterioration in renal function within 48 hours of the intravascular administration of a contrast compound. PC-AKI is a correlative diagnosis and PC-AKI may occur regardless of whether the administered contrast medium was the cause of the deterioration.^{38,39} The term contrast-induced acute kidney injury (CI-AKI) is reserved for cases where a causal relation can be shown between the administered contrast and the deterioration in renal function. However, in clinical practice it is usually difficult to distinguish CI-AKI from PC-AKI and very few of the published studies have a suitable control group to allow the two conditions to be separated. Thus, many cases of PC-AKI seen in clinical practice or reported in clinical studies are likely to be coincident to, but not caused by, contrast administration. PC-AKI is defined when one of the following criteria is met:

- Serum creatinine rises by ≥ 26 micromoles (μmol)/l within 48 hours
- Serum creatinine rises ≥ 1.5 fold from the baseline value, which is known or presumed to have occurred within one week
- Urine output is < 0.5 ml/kg/hour for more than six consecutive hours
- If a baseline serum creatinine is not available within one week, the lowest serum creatinine value recorded within three months of the episode of AKI can be used.

If a baseline serum creatinine value is not available within three months and AKI is suspected:

- Repeat serum creatinine within 24 hours
- A reference serum creatinine value can be estimated from the nadir serum creatinine value if the patient recovers from AKI.

Appendix 2.
**Chronic kidney
disease stages²⁶**

Chronic kidney disease (CKD) stage	GFR ml/min/1.73 m ²	Description
1	90+	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease.
2	60–89	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease.
3A	45–59	Moderately reduced kidney function.
3B	30–44	
4	15–29	Severely reduced kidney function.
5	<15 or on dialysis	Very severe or end-stage kidney failure (sometimes called established renal failure).

Appendix 3. Clinical features and clinicopathological definition of NSF

Clinical features of NSF

Initial presentation

- Pain
- Pruritus
- Swelling
- Erythema
- Usually starts in the legs.

Later results

- Thickened skin and subcutaneous tissues – ‘woody’ texture and brawny plaques
- Fibrosis of internal organs; for example, muscle, diaphragm, heart, liver, lungs
- Contractures
- Cachexia
- Death, in a proportion of patients.

At-risk patients

Higher risk

- Patients with chronic kidney disease (CKD) 4 and 5 (Appendix 2) (glomerular filtration rate [GFR] <30 ml/min/1.73 m²)
- Acute renal failure
- 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/1.73 m²)
- Children under one year (immature renal function).

Notes:

1. No cases of NSF have been reported in patients with GFR greater than 60 ml/min/1.73 m² at the time of administration and it appears that those few cases reported with estimated GFR above 30 were actually in acute renal failure when an estimated GFR is inappropriate.
2. The role of various possible co-factors in the pathogenesis of NSF is not proven but there are suspicions that both hyperphosphataemia and the use of erythropoietin may have a bearing.
3. In the absence of specific information, it remains wise to manage pregnant patients (whatever their renal function) in the same way as children aged less than one year in order to protect the fetus.

Clinicopathological definition of NSF (Girardi criteria)²⁹

The diagnosis of NSF is made with a combination of clinical and pathological scoring. For the clinical score there are major criteria (patterned plaques, joint contractures, cobblestoning and marked induration/peau d'orange) and minor criteria (skin puckering/banding, superficial NSF, dermal papules and scleral plaque in patients aged over 45). A clinical score is then summated with:

>1 major – highly consistent = 4

1 major – consistent = 3

>1 minor – suggestive = 2

0–1 minor = 1

Another diagnosis = 0

The pathology score follows a similar system for which the interested reader can find details in the referred original article.²⁸

Pathology/clinical⁴⁰

	0	1	2	3	4
0	Alternative diagnosis (Dx)				
1		Not NSF	Not NSF		Inconsistent
2			Suggestive	Consistent	
3			Consistent	NSF	
4		Inconsistent			

Appendix 4.
European Medicines Agency classification of gadolinium-based contrast agents²²

NSF risk category	Generic name	Trade name	T1 specific relaxivity in blood at 1.5 T – $\text{mmol}^{-1} \text{s}^{-1}$	Notes
High	Gadopentate dimeglumine	Magnevist (Bayer) plus generic products such as Magneqita (Agfa)	4.3	<ul style="list-style-type: none"> NSF – triggering agent, estimated to be 0.1–1% in at risk subjects (221 unconfounded cases – 2014 data). Now withdrawn from intravascular use following 2017 EMA decision. Intra-articular formulation remains available.
	Gadodiamide	Omniscan, GE Healthcare	4.6	<ul style="list-style-type: none"> NSF – triggering agent, estimated 3–7% in at-risk subjects (624 unconfounded cases – 2009 data). Now withdrawn from intravascular use following 2017 EMA decision.
	Gadoversetamide	OptiMARK, Guerbet – previously Mallinckrodt	5.2	<ul style="list-style-type: none"> NSF – triggering agent, no clear data but five reported cases, likely similar incidence to gadodiamide, to which it is chemically related. Now withdrawn from intravascular use following 2017 EMA decision.

NSF risk category	Generic name	Trade name	T1 specific relaxivity in blood at 1.5 T – $\text{mmol}^{-1} \text{s}^{-1}$	Notes
Medium	Gadobenate dimeglumine	MultiHance	6.7	<ul style="list-style-type: none"> ▪ Ionic linear chelate, 2–3% protein binding, significant hepatic excretion. ▪ NSF – single unconfounded report that does not meet Girardi criteria ▪ Indication now limited to liver imaging and when imaging in the delayed phase is required – this would include protocols where dynamic imaging involving acquisition of arterial phases is combined with delayed phase scans.
	Gadoxetate disodium	Primovist	8.7	<ul style="list-style-type: none"> ▪ Ionic linear chelate, 10% protein binding and 50% hepatic excretion. ▪ Incidence of NSF – no reports of NSF. ▪ Indication now limited to liver imaging and when imaging in the delayed phase is required – this would include protocols where dynamic imaging involving acquisition of arterial phases is combined with delayed phase scans.

NSF risk category	Generic name	Trade name	T1 specific relaxivity in blood at 1.5 T – $\text{mmol}^{-1} \text{s}^{-1}$	Notes
Low	Gadobutrol	Gadovist	5.3	<ul style="list-style-type: none"> Non-ionic chelate. NSF – four unconfounded reports but unclear as to whether they meet Girardi criteria.
	Gadoterate meglumine	Dotarem	4.2	<ul style="list-style-type: none"> Ionic cyclic chelate. NSF – no unconfounded reports.
	Gadoteridol	Prohance	4.4	<ul style="list-style-type: none"> Non-ionic chelate. NSF – single unconfounded report, unclear as to whether it meets Girardi criteria.

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