Please note that this is a rapidly changing area and the following guidance will be kept under frequent review.
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Overview

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. Information on the risk of NSF and Gd-CM has been published by the Medicines and Healthcare products Regulatory Agency (MHRA).¹,²

Information about NSF continues to be collected and it is very important that:

- A record is always kept of the type and amount of each injection of Gd-CM given
- All cases of NSF should be reported to the MHRA via the Yellow Card scheme.³

As new information becomes available, it may be necessary to revise this overview and guideline.

Clinical features of NSF

Onset: From the day of exposure for up to two to three 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; for example, muscle, diaphragm, heart, liver, lungs.

Result

- Contractures
- Cachexia
- Death, in a proportion of patients.

At-risk patients

Higher risk

- Patients with chronic kidney disease (CKD) 4 and 5 (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, because of their immature renal function.
Note:

1. No cases of NSF have been reported in patients with GFR greater than 60 ml/min/1.73 m\(^2\).
2. The role of various possible co-factors in the pathogenesis of NSF is not proven.
3. In the absence of specific information, it seems wise to manage pregnant patients, whatever their renal function, in the same way as children aged less than one year to protect the fetus.

Screening for renal dysfunction 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.
- Screening for renal dysfunction is mandatory before using Gd-CM agents associated with NSF (such as Omniscan, Magnevist, OptiMark). This can be done by measuring serum creatinine (which can be used to estimate GFR employing the Modification of Diet in Renal Disease study [MDRD] formula or Cockroft-Gault equation or via a questionnaire (such as history of renal disease, prior kidney surgery, hypertension, gout, diabetes mellitus or age ≥65 years; if the answer is yes to any of these questions serum creatinine levels should be obtained).\(^4\)

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/1.73m\(^2\))
  - Always use the smallest possible amount of the contrast agent to achieve an adequate diagnostic examination.
  - Never use gadolinium as a contrast agent for radiography, computed tomography, or angiography as a method of avoiding nephropathy associated with iodinated contrast media.

Immediate haemodialysis after administration of Gd-CM

- At least nine hours of haemodialysis (three 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.
Use in paediatric cases

The principles of the guidelines on reducing the risk of NSF in adult patients are also applicable for paediatric cases. However, please note that some Gd-CM preparations are not licensed for paediatric use. Off-label use of CM should be clinically justified, supported by published data in scientific journals and on a named patient basis under local protocol arrangements.
# Guidelines for use of gadolinium chelates

<table>
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<th>Definition</th>
<th>Nephrogenic systemic fibrosis (NSF) is a severe delayed fibrotic reaction of the tissues to some gadolinium-based contrast media (Gd-CM)</th>
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</table>
| **1. Clinical features** | • NSF may develop from the day of exposure for up to 2–3 months  
• Starts with red, painful, itchy swellings on the legs and arms  
• May be localised and non-progressive  
• May progress to extensive fibrotic lesions of the skin and subcutaneous tissues and sometimes of the internal organs  
• Fatal in a proportion of cases |
| **2. Patient-related risk factors** | • Renal impairment (GFR <60 ml/min/1.73²), including patients on dialysis  
• Liver transplant patients who had or are waiting for a transplantation with any degree of renal impairment  
• Age under one year, because of immature renal function.  
*Note:*  
1. NSF has not been reported in patients with GFR >60 ml/min/1.73m²  
2. The role of other possible co-factors is not proven. |
| **3. Contrast medium-related risk factors** | • Less stable Gd-CM (linear agents)  
• NSF has occurred following the administration of:  
  − Omniscan (gadodiamide, linear chelate)  
  − Magnevist (gadopentetate dimeglumine, linear chelate)  
  − OptiMARK (gadoversetamide, linear chelate). |
| **4. Screening for renal dysfunction before Gd-CM** | • Mandatory if considering the use of Gd-CM associated with the development of NSF (Omniscan, Magnevist, OptiMARK) |
| **5. To reduce the risk of NSF in MR examinations in definably at-risk patients (See 2 for at-risk patients)** | • Use a GD-CM with high stability (Please see Appendix 1)  
• Give the lowest dose possible to achieve a diagnostic examination  
• Allow at least one week before giving more Gd-CM  
• Do not use Omniscan (gadodiamide); Magnevist (gadopentetate dimeglumine) or OptiMARK (gadoversetamide).  
*Note:* Do not deny at-risk patients clinically important MR examinations. |
| **6. Radiographic examinations** | • Do not use Gd-CM for X-ray examinations⁵ |
| **7. Pregnant patients** | If the use of a Gd-CM agent is essential, whatever the maternal renal function, choose the most stable Gd-CM in the lowest possible dose to protect the fetus. |
Acknowledgements

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Appendix 1

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 much higher stability in comparison to linear chelates. Current knowledge about the properties of the different agents and the incidence of NSF when they are used in at-risk patients are summarised below. Products are presented in alphabetical orders 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 in**
- Patients with CKD 4 and 5 (GFR <30 ml/min/1.73m²), including those on dialysis
- Patients with reduced renal function who have had or are awaiting liver transplantation
**USE WITH CAUTION in**
- Patients with CKD 3 (GFR 30–60 ml/min/1.73m²)
- 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 hours compared to 1½ hours, respectively).
*S-creatinine (eGFR) measurement:* Not mandatory

**Gadopentetate dimeglumine (Magnevist®)**
*Ligand:* Ionic linear chelate (DTPA)
*Incidence of NSF:* Estimated to be 0.1 to 1 % in at risk subjects
**S-creatinine (eGFR) measurement**: Mandatory.

**Haemodialysis**: Gadopentate dimeglumine is contraindicated in patients on dialysis.

**CONTRAINDICATED in**
- Patients with CKD 4 and 5 (GFR <30 ml/min/1.73m²), including those on dialysis
- Patients with reduced renal function who have had or are awaiting liver transplantation

**USE WITH CAUTION in**
- Patients with CKD 3 (GFR 30–60 ml/min/1.73m²)
- 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**: One case of mild localised NSF in a patient with severe renal impairment.
- **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 in**
  - Patients with CKD 4 and 5 (GFR <30 ml/min/1.73m²), including those on dialysis
  - Patients with reduced renal function who have had or are awaiting liver transplantation
- **USE WITH CAUTION in**
  - Patients with CKD 3 (GFR 30–60 ml/min/1.73m²)
  - Children less than 1 year old.

**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

**Definitions**

**Unconfounded**: In ‘unconfounded’ cases only one Gd-CM had been given before NSF developed.

**Confounded**: If two different Gd-CM agents had been injected within eight weeks of each other (may be 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 agent.

**Chronic kidney disease (CKD)**
CKD 1: GFR >90 ml/min/1.73m²
CKD 2: GFR 60–90 ml/min/1.73m²
CKD 3: GFR 30–60 ml/min/1.73m²
CKD 4: GFR 15–30 ml/min/1.73m²
CKD 5: GFR <15 ml/min/1.73m² and/or peritoneal or haemodialysis
References


7. Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: is the stability of the contrast molecule an important factor in the pathogenesis of this condition? *Br J Radiol* 2007; 80: 73–76.

Further reading


