

# **ESUR GUIDELINE\*: GADOLINIUM BASED CONTRAST MEDIA AND NEPHROGENIC SYSTEMIC FIBROSIS** (17 July 2007)

## **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 about NSF continues to be collected.

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 are reported to the National Regulatory Authority.

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 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, eg 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 < 30ml/min )
- Patients on dialysis

- Patients with reduced renal function who have had or are awaiting liver transplantation

#### Lower risk

- Patients with CKD 3 (GFR 30-59ml/min)
- Children under 1 year, because of their immature renal function

NOTE:1. No cases of NSF have been reported in patients with *GFR greater than 60ml/min*

2.The role of various *possible cofactors* in the pathogenesis of NSF is not proven.

3. *Pregnant patients*. In the absence of specific information, it seems wise to manage pregnant patients, whatever their renal function, in the same way as children aged under 1 year to protect the fetus.

### **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 before Gd-CM is mandatory before Gd-CM which have been associated with subsequent development of NSF
- Measurement of serum creatinine/ eGFR is not necessary in all patients receiving Gd-CM.

### **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 preorganized rigid rings of almost optimal size to cage the gadolinium ion which 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 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

*Hemodialysis:* Gadodiamide is contraindicated in patients on dialysis.

CONTRAINDICATED in

- 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 in

- 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 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.

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

CONTRAINDICATED in

- 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 in

- 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.

*Hemodialysis:* Gadoversetamide is contraindicated in patients on dialysis.

CONTRAINDICATED in

- 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 in

- patients with CKD 3 (GFR 30-60 ml/min )
- 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

\* See definitions below.

### IMMEDIATE HEMODIALYSIS AFTER ADMINISTRATION OF Gd-CM

- At least 9 hours of hemodialysis (3 sessions) is required to remove a Gd-CM. The efficacy of hemodialysis can be variable and depends on many factors.
- There is no evidence that immediate hemodialysis 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 hemodialysis for the sole purpose of removing a Gd-CM is not recommended in patients who have not already been stabilized on hemodialysis 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.

## **DEFINITIONS:**

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

*Confounded:* If two different Gd-CM had 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 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/1.73m<sup>2</sup>

CKD 2 : GFR 60-90 ml/min/1.73m<sup>2</sup>

CKD 3 : GFR 30-60 ml/min/1.73m<sup>2</sup>

CKD 4 : GFR 15-30 ml/min/1.73m<sup>2</sup>

CKD 5 : GFR <15 ml/min/1.73m<sup>2</sup> and/or peritoneal or hemodialysis

## Guideline: Nephrogenic Systemic Fibrosis (NSF)

<b>Definition</b>	Nephrogenic systemic fibrosis (NSF) is a severe delayed fibrotic reaction of the body tissues to some Gadolinium–based contrast media (Gd-CM)
<b>Clinical Features</b>	<ul style="list-style-type: none"> <li>• NSF may develop from the day of exposure for up to 2-3 months</li> <li>• Starts with red, painful, itchy swellings on the legs and arms</li> <li>• Progresses to fibrotic lesions of the skin and subcutaneous tissues and sometimes of the internal organs</li> <li>• Fatal in a proportion of cases</li> </ul>
<b>Risk Factors: <i>Patient related</i></b>	<ul style="list-style-type: none"> <li>• Renal impairment, including patients on dialysis</li> <li>• Age under 1 year, because of immature renal function.</li> </ul> <p><i>Note:</i> 1. NSF has not been reported in patients with GFR greater than 60ml/min 2. The role of other possible cofactors is not proven.</p>
<b>Contrast Medium related</b>	<ul style="list-style-type: none"> <li>• Less stable Gd-CM</li> <li>• NSF has occurred following the administration of: Gadodiamide Gadopentetate dimeglumine Gadoversetamide</li> </ul>
<b>Measurement of serum creatinine before Gd-CM</b>	<ul style="list-style-type: none"> <li>• Not necessary in all patients</li> <li>• Mandatory if considering the use of Gd-CM associated with the development of NSF.</li> </ul>
<b>To reduce the risk of NSF in at risk patients: <i>MR examinations</i></b>	<ul style="list-style-type: none"> <li>• Use a GD-CM not associated with the development of NSF</li> <li>• Give the lowest dose possible to achieve a diagnostic examination</li> <li>• Allow at least one week before giving more Gd-CM</li> <li>• Do not use Gadodiamide Gadopentetate dimeglumine Gadoversetamide</li> </ul> <p><i>Note:</i> Do not deny at risk patients clinically important MR examinations.</p>
<b>Radiographic examinations</b>	<ul style="list-style-type: none"> <li>• Do not use Gd-CM for radiographic examinations</li> </ul>
<b>Pregnant patients</b>	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.

### ***Suggested further reading:***

- Broome DR, Girguis M, Baron P, Cottrel A, Kjellin I, Kirk G. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR* 2007;188:586-592.
- Center for Disease Control and Prevention (CDC). Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents – St. Louis, Missouri, 2002-2006. *MMWR Morb Mortal Wkly Rep* 2007;56:137-41.
- Collidge TA, Thompson PC, Mark PB et al. Gadolinium-enhanced magnetic resonance imaging and nephrogenic systemic fibrosis – a retrospective case-control study. *Radiology* 2007: in press.
- Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. *CJASN* 2007; 2: 264-267.
- EMEA decision of 26.06.07. Available through [www.esur.org](http://www.esur.org). Assessed XX.XX.XX
- Grobner T. Gadolinium - a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006;21:1104-1108.
- High W, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 2007;56:27-30.
- Idée J-M, Port M, Raynal I, Schaefer, Le Greneur S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fundam Clin Pharmacol* 2006;20:563-576.
- Khurana A, Runge VM, Narayanan M, Greene JF, Nickel AE. Nephrogenic systemic fibrosis. A review of 6 cases romporally related to gadodiamide injection (Omniscan). *Invest Radiol* 2007;42:139-145,
- Maloo M, Abt P, Kashyap R et al. Nephrogenic systemic fibrosis among liver transplant recipients: A single institution experience and topic update. *Am J Transpl* 2006;6:2212-2217.
- Marckmann P, Skov L, Rossen K et al. Nephrogenic systemic fibrosis: Suspected etiological role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006;17: 2359-2362.
- Morcos, S.K. Nephrogenic systemic fibrosis following the administratrion of extracellular gadolinium based contrast agents: is the stability of the contrast molecule an important factor in the pathogenesis of this condition? *Brit J Radiol* 2007: 2007; 80: 73-76
- Sadowski E, Bennett LK, Chan MR et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; 43: 148-157
- Thomsen HS. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. *Eur Radiol* 2006;16:2619-2621.
- Thomsen HS, Almén T, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology. Gadolinium-containing contrast media for radiographic examinations: a position paper. *Eur Radiol* 2002;12:2600-2605.
- Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). In which patients should serum-creatinine be measured before contrast medium administration? *Eur Radiol* 2005;15;749-754.

---

\* The content of this document presents the consensual opinion of **only** the Academic members of the ESUR Contrast Media Safety Committee.