# Guidance on gadolinium based contrast agent administration to adult patients, fifth edition

## 1. Recommendations

The key recommendations outlined in this guidance are as follows:

### Pre procedure

1. The general safety recommendations are similar to those of iodine based contrast media and this document should be used alongside the adopted Royal Australian and New Zealand College of Radiologists (RANZCR) Iodinated Contrast Media Guidelines.[1]
2. The dose of gadolinium-based contrast agent (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.
3. GBCAs should be used with caution and dose minimised in patients with severe chronic or acute renal impairment, and in patients in the peri-operative liver transplantation period.
4. The risks of NSF with the newer macrocyclic agents are vanishingly low with no unconfounded cases in the modern era. However, when using GBCAs knowledge of the patient's renal functional status is advisable.

### Peri-procedure

5. GBCAs are associated with a very low rate of immediate hypersensitivity reactions. For management of these, please see RANZCR guidelines section 4 Management of anaphylactic iodine based contrast media (ICBM) reaction.[1]

### Post procedure

6. 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.
7. Delayed contrast reactions are rare, but these should be fully investigated and recorded.

## 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.[2] Gadolinium based contrast agents (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 i.e., 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, the original linear chelates such as DTPA were later supplemented by macrocyclic chelate compounds which are magnitudes of order more stable.

There has been a huge increase in the use of GBCAs in radiology since their commercial introduction. Indeed, worldwide there are currently nearly 60 million patient administrations per

year, perhaps 1 in 3 of all MRI studies.[3] In the main this is due to their clinical utility balanced against their excellent safety record.

## Pre-Procedure planning:

## Prescribing Contrast

A formal record of the decision to inject an intravascular contrast agent 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 assignation process
- A formal prescription on the patient's drug chart.

## 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.

## General Safety Issues

GBCAs are associated with a very low rate of immediate adverse events (0.06% - 0.09%).[18,19] Most acute 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%.[4,5]

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. The same principles apply to that of ICBM use (please see RANZCR guidance 3 general safety issues).

## 3. Recommendations for Contrast Agent use in Patients at Increased Risk of an Immediate Hypersensitivity Reaction

The Same principles apply as ICBM please refer to RANZCR guidelines section 2 'Risk assessment and management of patients prior to iodine based contrast media administration'.[1]

## 4. Recommendations for Contrast Agent use in Patients with Renal disease and conditions associated with Renal Impairment

GBCAs are remarkably safe, with lower adverse event rates for both allergic type reactions and nephrotoxicity than IBCM. However, high volumes of GBCAs are potentially nephrotoxic and in the presence of renal impairment there is theoretical potential for Post-Contrast Acute Kidney Injury (PC-AKI), in clinical practice this seems to be extremely rare with only a single case report from 2004 in a patient with prior severe renal impairment administered GBCA (Gadodiamide) suffering a deterioration in renal function requiring dialysis.[6]

However, the administration of the non-specific linear chelate agents, particularly in patients with severe renal failure was historically associated with the development in some of the very rare condition nephrogenic systemic fibrosis (NSF). The advice below is to minimise this risk from GBCAs in vulnerable groups.

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.[7]

### Renal Impairment

For patients with severe chronic renal impairment (eGFR <30 ml/ min/1.73 m2) or acute renal impairment requiring MRI thought to necessitate GBCA enhancement then if, following clinical review it is indeed necessary to use a GBCA (either a low-risk macrocyclic agent or, if required the use of a medium-risk agent for specific liver imaging - see appendix 4); the lowest dose possible should be used (a dose not exceeding 0.1 millimoles per kilogram [mmol/kg] body weight) and this should not be repeated for at least seven days. If possible, avoidance of administering GBCAs in patients with acute kidney injury while creatinine is rising is preferrable. For patients with severe chronic renal impairment (eGFR <30 ml/ min/1.73 $m^2$) or acute renal impairment requiring gadolinium injection following clinical review, use of a low-risk agent is appropriate or if necessary a use a medium-risk agent (See appendix 4); the lowest dose possible should be used (a dose not exceeding 0.1 millimoles per kilogram [mmol/kg] body weight) and this should not be repeated for at least seven days. If possible, avoidance of administering GBCAs in patients with acute kidney injury while creatinine is rising is preferrable.

Similarly, for patients with moderate chronic renal impairment (eGFR 30–59 ml/ min/1.73 $m^2$), if, after review, it is necessary to use a GBCA then the single lowest dose possible should be used and this should not be repeated for at least seven days.

### Perioperative liver transplantation period

If the use of a low-risk macrocyclic GBCA is required (or if it is necessary to use a medium-risk GBCA 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; this is because emergency initiation of dialysis entails significant risks. However, those patients already established on dialysis can have their dialysis scheduled to follow contrast agent administration (within 24 hours).[8]

## 5. Recommendations for Contrast Agent use during Pregnancy and Lactation

### Pregnancy

There is little human data regarding the use of GBCAs in pregnant women.[9] While animal data and the limited observational human literature are very reassuring as regards any potential effects of 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 foetus 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 infant gut. No special precaution or cessation of breastfeeding is required.[10]

## Miscellaneous Considerations

Large volumes of GBCAs (>30ml) 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 angiography or CT. Small volumes of GBCA's (< 30 ml) may however be considered in invasive angiography in exceptional circumstances where there is confirmed severe allergy to iodinated contrast media. Previous terminology such as contrast nephrotoxicity, contrast-induced nephropathy (CIN) or radiocontrast nephropathy (RCN) have been replaced by Contrast-Associated Acute Kidney Injury (CA-AKI), in line with other causes of acute kidney injury.[9,10] (See Appendix 1 for definitions of AKI).

There is no need to stop metformin after GBCA administration.

## Immediate complications : Contrast Media Extravasation (CMEx) (See also RANZCR guidelines 3.1)

The incidence of CMEx with GBCAs is extremely and reported as approximately 0.06% (significantly less than the rates with IBCM) with no serious complications described.[11] This is likely due to low infusion rates and lower CM volumes compared to those required for IBCM.

## Acute Adverse Reactions

GBCAs are associated with a very low rate of immediate hypersensitivity reactions and the incidence of acute, severe reactions is estimated to be just 0.0025% - 0.005%.[12,13]

Guidelines for the treatment of acute reactions are as for IBCM , see RANZCR guidance section 4 management of anaphylactic iodine based contrast media reactions.[1]

## Post Procedure

## Late Adverse Reactions

The incidence of NIHR following GBCA use is also very low, best estimate is 0.05%. While GBCAs are potentially nephrotoxic, similar to IBCM in equimolar quantities, the clinically approved small amounts used means that nephrotoxicity is not generally a clinical issue.[14]

## Very Late Adverse Reactions

The very rare condition nephrogenic system fibrosis (NSF) and more recent concerns regarding the issue of gadolinium deposition or retention prompted a review of the different agents which, in Europe, were subsequently classified by the European Medicines Agency on perceived risk. Subsequent restrictions were imposed on the intravascular use of linear chelate GBCAs while the macrocyclic chelate GBCAs (with the lowest potential for dechelation) are less constrained – see Appendix 1.

The potential and theoretical risks of intravascular administration of GBCAs must be weighed against the potential benefits for the patient. Withholding contrast 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 in adult patients. For children and neonates, a paediatric radiologist should be consulted.

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).

## 6. Conclusion

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

## References


1 www.ranzcr.com/college/document-library/iodinated-contrast-guidelines-2016?searchword=odinated%20guidelines

2 Gadolinium-DTPA as a contrast agent in MRI: initial clinical experience in 20 patients. Carr DH, Brown J, Bydder GM, et al. AJR Am J Roentgenol. 1984;143(2):215–24

3 Lohrke J, Frenzel T, Endrikat J et al. 25 years of contrast-enhanced MRI: Developments, current challenges and future perspectives. Adv Ther 2016; 33(1): 1–28.

4 Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. Radiology 2018; 286(2): 471–482.

5 Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. AJR Am J Roentgenol 2011; 196(2): W138–W143.

6 National Institute for Health and Care Excellence. *NICE clinical guidelines (CG169): acute kidney injury: prevention, detection and management.* London: National Institute of Health and Care Excellence, 2013.

7 www.gov.uk/drug-safety-update/gadolinium-containing-contrast-agents-new-advice-to-minimise-the-risk-of-nephrogenic-systemic-fibrosis#:~:text=Advice%20for%20healthcare%20professionals,risk%20or%20low%2Drisk%20agents. (last accessed 11/3/24)

8 Zou Z, Zhang HL, Roditi GH et al. Nephrogenic systemic fibrosis: review of 370 biopsy – confirmed cases. JACC Cardiovasc Imaging 2011; 4 (11): 1,206–1,216.

9 Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA 2016; 316(9): 952–961.

10 www.rcr.ac.uk/news-policy/latest-updates/rcr-and-sor-statement-on-patients-who-are-breastfeeding-who-require-a-ct-or-mri-with-contrast/#:~:text=Position%20statement%20%E2%80%93%20for%20patients&text=It%20is%20the%20view%20of%20both%20the%20RCR%20and%20the,risk%20to%20the%20baby%2Fchild.

11 Roditi G, Khan N, van der Molen AJ *et al*. Clément OIntravenous contrast medium extravasation: systematic review and updated ESUR Contrast Media Safety Committee Guidelines. *Eur Radiol*. 2022 May;32(5):3056-3066.

12 Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. Radiology 2018; 286(2): 471–482.

13 Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. AJR Am J Roentgenol 2011; 196(2): W138–W143.

14 van der Molen AJ, Reimer P, Dekkers IA et al. Post-contrast acute kidney injury – Part 1: Definition, clinical features, incidence, role of contrast medium and risk factors. Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol 2018; 28(7): 2,845–2,855.

## Appendix 1: Very Late Adverse Reactions & Regulation

In 2006 the association between the administration of GBCAs to patients with severe renal failure and the development of the very rare condition nephrogenic system fibrosis (NSF) came to light.[15,16] This prompted a review of the different GBCAs which in Europe were subsequently classified by the European Medicines Agency on the perceived risk of dissociation that aligned with those compounds most frequently associated with the development of NSF. 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.

Because of the response of the radiology community, avoiding use of the less stable linear chelate 'high risk' GBCAs in those patients known to be at greatest risk for NSF (i.e. those with renal severe failure), no new cases related to exposure to the agents following the restrictions were reported except for a single isolated case in the USA of NSF associated with the mistaken administration of high risk linear GBCA to a patient with sepsis on haemodialysis, against departmental SOPs.[17] There have, however, been reported cases of NSF manifesting subsequent to the changes where the association has been to the administration of 'high risk' GBCAs to patients with severe renal failure prior to the FDA warning of 2007 with the development of NSF years later, although the reasons for these delayed manifestations are obscure.[17,18]

A more recent concern has been the issue of gadolinium deposition or retention on which there has been much research. This followed a series of publications investigating signal hyperintensity on unenhanced T1 weighted MRI of the brain (involving the dentate nucleus and basal ganglia especially) in patients that had previously been administered multiple doses of linear chelate GBCAs, which indicated that there may be long term gadolinium deposition in the brain.[19,20] This brain deposition, albeit in tiny amounts, has been subsequently confirmed in cadaver studies.[21,22]

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). Deposition in the brain is in even lower concentrations than other parts of the body and has been shown to be orders of magnitude lower for the macrocyclic agents than the linear agents.[23,24] 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.[25] Studies in the 10 plus years since the first reports have been reassuring with no evidence of clinical symptoms nor associated harm related to this deposition.[26]

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) commenced an investigation into the concerns regarding gadolinium retention/deposition following administration of GBCAs. Following this and a consultation process, although there is currently no evidence that gadolinium deposition in the brain has caused adverse neurological effects to patients, the marketing authorisations of some linear chelate GBCAs were withdrawn while others were amended by the Committee for Medicinal Products for Human Use (CHMP).

## Appendix 2: Contrast associated acute kidney injury

Contrast-associated acute kidney injury (CA-AKI) (formerly known as post-contrast acute kidney injury (PC- AKI)) is a general term used to describe a sudden deterioration in renal function that occurs within 48 hours following the intravascular administration of a contrast medium. CA-AKI may occur regardless of whether the contrast medium was the cause of the deterioration. CA-AKI is a correlative diagnosis.[27,28] 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 CA-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 CA-AKI seen in clinical practice or reported in clinical studies are likely to be coincident to, but not caused by, contrast administration. CA-AKI is defined when one of the following criteria is met.

- Serum creatinine rises by ≥26 micromoles per litre (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 3. Chronic kidney disease stages[29]

| Chronic kidney disease (CKD) stage | GFR ml/min/1.73 m2 | 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 |
| 3A<br>3B | 45–59<br>30–44 | Moderately reduced kidney function |
| 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 4. Clinical features and clinicopathological definition of NSF

NSF was 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. Some patients with NSF had 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 was 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).[30] 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 even present years later.[18,31]

In 2017 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) suspended the linear chelates thought to be highest risk from intravascular use.

The EMEA's Scientific Advisory Group on Diagnostics have 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 macrocyclic GBCAs in patients with renal impairment because, in some cases, there are no alternatives (although the 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.

### Notes:

1. No cases of NSF have been reported in patients with GFR greater than 60 ml/min/1.73 $m^2$ 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 foetus.

### Clinicopathological definition of NSF (Girardi criteria)[30]

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, cobble stoning 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

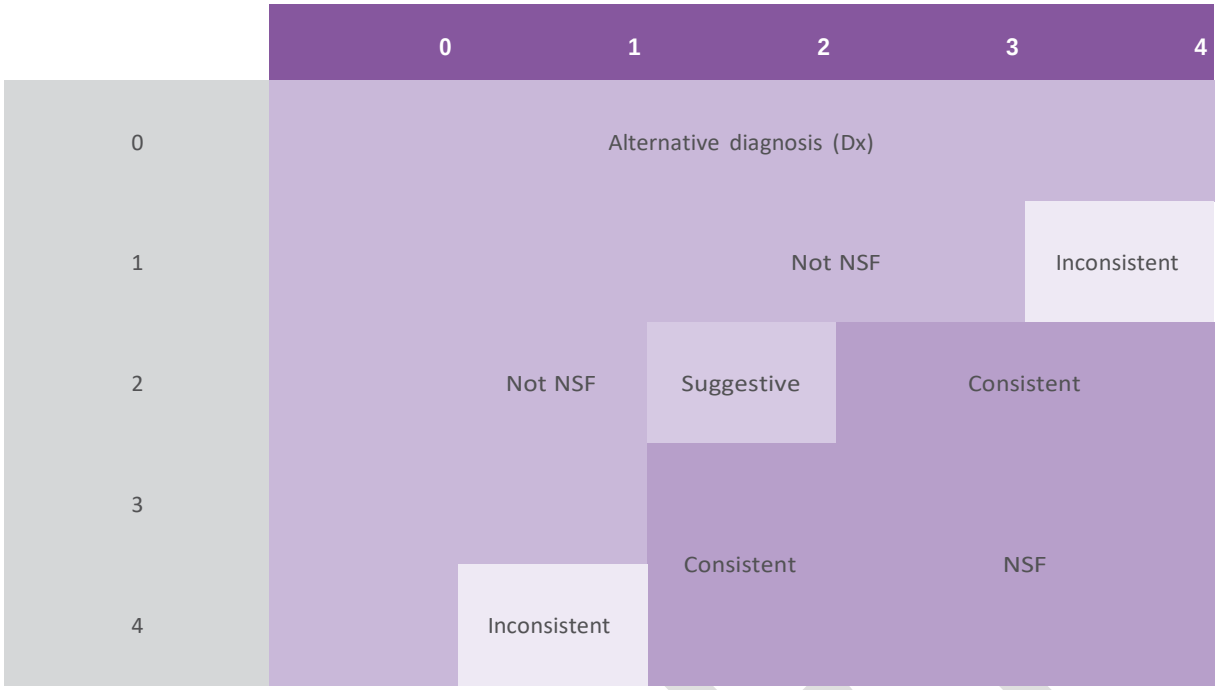
>1 Minor – Suggestive = 2

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.[30]

**Pathology/clinical**



## European Medicines Agency classification of gadolinium-based contrast agents[32]

The following agents are correct as of the date of publication, but newer agents may become available over time.

| NSF risk category | Generic name | Trade name | T1 specific relaxivity in blood at 1.5 T | Notes |
|---|---|---|---|---|
| High | Gadopentate dimeglumine | Magnevist (Bayer) plus generic products such as Magnegita (Agfa) | 4.3 | • NSF– triggering agent, estimated to be 0.1–1% in at risk subjects (221 unconfounded cases – 2014 data).<br>• **Now withdrawn from intravascular use following 2017 EMA decision**<br>• Intra-articular formulation remains |
| | Gadodiamide | Omniscan, GE Healthcare | 4.6 | • NSF – triggering agent, estimated 3–7% in at-risk subjects (624 unconfounded cases – 2009 data).<br>• **Now withdrawn from intravascular use following 2017 EMA decision** |
| | Gadoversetamide | OptiMARK, Guerbet – previously Mallinckrodt | 5.2 | • NSF – triggering agent, no clear data but five reported cases, likely similar incidence to gadodiamide, to which it is chemically related.<br>• **Now withdrawn from intravascular use following 2017 EMA decision.** |
| Medium | Gadobenate dimeglumine | MultiHance | 6.7 | • Ionic linear chelate, 2–3% protein binding, significant hepatic excretion.<br>• NSF – single unconfounded report that does not meet Girardi criteria<br>• 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 | • Ionic linear chelate, 10% protein binding and 50% hepatic excretion.<br>• Incidence of NSF – no reports of NSF<br>• 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 |
| Low | Gadobutrol | Gadovist | 5.3 | Non-ionic cyclic chelate.<br>• NSF – four unconfounded reports but unclear as to whether they meet Girardi criteria. |
| | Gadoterate meglumine | Dotarem | 4.2 | Ionic cyclic chelate.<br>• NSF – no unconfounded reports. |
| | Gadoteridol | Prohance | 4.4 | Non-ionic cyclic chelate.<br>• NSF – single unconfounded report, unclear as to whether it meets Girardi criteria. |

## References


15 Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplan*t 2006; **21**(4): 1,104–1,108.

16 Marckmann P, Skov L, Rossen K *et al*. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006; **17**(9): 2,359–2,362.

17 Bennett CL, Quereshi ZP, Sartor AO *et al.* Gadolinium-induced nephrogenic systemic fibrosis: the rise and fall of an iatrogenic disease. *Clin Kidney J* 2012; **5**(1): 82–88

18 Do JG, Kim YB, Lee DG and Hwang JH. A case of delayed onset nephrogenic systemic fibrosis after gadolinium based contrast injection. *Ann Rehabil Med* 2012; **36**(6): 880–886.

19 Kanda T, Ishii K, Kawaguchi H, Kitajima K and Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology* 2013; **270**(3): 834–841.

20 Errante Y, Cirimele V, Mallio CA *et al*. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. *Invest Radiol* 2014; **49**(10): 685–690.

21 Kanda T, Fukusato T, Matsuda M *et al.* Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology* 2015; **276**(1): 228–232.

22 McDonald RJ, McDonald JS, Kallmes DF *et al.* Intracranial gadolinium deposition after contrastenhanced MR imaging. *Radiology* 2015; **275**(3): 772–782.

23 Radbruch A, Weberling LD, Kieslich PJ *et al*. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology* 2015; **275**(3): 783–791

24 Murata N, Gonzalez-Cuyar LF, Murata K *et al.* Macrocyclic and other non-group 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: preliminary results from 9 patients with normal renal function. *Invest Radiol* 2016; **51**(7): 447–453.

25 Frenzel T, Apte C, Jost G *et al*. Quantification and assessment of the chemical form of residual gadolinium in the brain after repeated administration of gadolinium-based contrast agents: comparative study in rats. *Invest Radiol* 2017; **52**(7): 396–404.

26 Welk B, McArthur E, Morrow SA *et al*. Association between gadolinium contrast exposure and the risk of parkinsonism. *JAMA* 2016; **316**(1): 96–98.

27 ACR Committee on Drugs and Contrast Media. ACR Manual on Contrast Media, version 2023. American College of Radiology 2023 via: https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf.

28 Post-contrast acute kidney injury – Part 1: Definition, clinical features, incidence, role of contrast medium and risk factors. Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. European Radiology. 2018; 28(7): 2845-2855.

29 Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**(4):
c179–c184.
30 Girardi M, Kay J, Elston DM *et al.* Nephrogenic systemic fibrosis: clinicopathological definition and
workup recommendations. *J Am Acad Dermatol* 2011; **65**(6): 1,095–1,106.
31 Thomson LK, Thomson PC, Kingsmore DB *et al*. Diagnosing nephrogenic systemic fibrosis in the post-
FDA restriction era. *J Magn Reson Imaging* 2015; **41**(5): 1,268–1,271.
32 Morcos SK, Thomsen HS, Webb JAW *et al*. Prevention of generalized reactions to contrast media: a
consensus report and guidelines. *Eur Radiol* 2001; **11**(9): 1,720–1,728.