GUIDELINE ON THE USE OF GADOLINIUM-CONTAINING MRI CONTRAST AGENTS IN PATIENTS WITH RENAL IMPAIRMENT

FACULTY OF CLINICAL RADIOLOGY

THE ROYAL AUSTRALIAN AND NEW ZEALAND COLLEGE OF RADIOLOGISTS®
This guideline is endorsed by the Dialysis, Nephrology and Transplant Sub-committee [DNT], which is the clinical working committee of both the Australian and New Zealand Society of Nephrology and Kidney Health Australia.

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1. INTRODUCTION

1.1 Purpose and scope

(a) The Guideline on the use of Gadolinium-containing MRI Contrast agents in patients with Renal Impairment has been developed by the College’s Standards of Practice and Accreditation Committee’s MRI Reference Group, in consultation with the Dialysis, Nephrology and Transplant Sub-committee of the Australian and New Zealand Society of Nephrology. It is designed to provide guidance to radiologists on the safe and effective use of contrast agents used to enhance Magnetic Resonance Imaging examinations.

(b) This guideline is a consensus based document and provides information on nephrogenic systemic fibrosis (NSF) and risk to patients when administering contrast agents. It also provides recommendations on screening protocol and risk mitigation strategies to provide the safest environment for patients during diagnostic imaging examinations, whilst still ensuring appropriate access to imaging when clinically indicated.

1.2 Definitions

In this Guideline:

**AKI** means Acute Kidney Injury

**ANZSN** means the Australian and New Zealand Society of Nephrology

**College** means The Royal Australian and New Zealand College of Radiologists.

**Member** means a member of the College.

**NSF** means Nephrogenic systemic fibrosis

1.3 College Mission

The College’s Mission is:

As a fellowship based organisation, The Royal Australian and New Zealand College of Radiologists sets, promotes and continuously improves the standards of training and practice in radiology and radiation oncology, for the betterment of the people of Australia and New Zealand.

2. NEPHROGENIC SYSTEMIC FIBROSIS

2.1 What is NSF

Nephrogenic systemic fibrosis (NSF) is a relatively uncommon condition in which fibrous plaques develop in the dermis and, often, in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of gadolinium-containing MRI contrast agents. The disease is often disabling, no proven treatments exist, and it may contribute to patient demise.
2.2 Who is at Risk

Whilst cases have occurred in patients with either acute or chronic renal failure, most have been in patients with chronic and severe kidney disease (CKD Stage 4 & 5, glomerular filtration rate (GFR) < 30 ml/ min/1.73 m²); most have been on dialysis. In Stage 5 CKD, a single exposure to gadodiamide (Omniscan) carries a risk in the order of 1 % of subsequent NSF - with gadopentetate [Magnevist], the risk has been estimated at 0.1 - 1 %. Two cases initially reported as having had “moderate” renal failure (nominally Stage 3 CKD, creatinine clearance 30 – 60 ml/min/1.73 m²) are now acknowledged as having had acutely deteriorating renal function at the time. Only a very small number of cases of NSF have been reported in patients with stable eGFR > 30ml/min/1.73 m² and in all these cases the eGFR was close to 30ml/min/1.73 m². Thus it is likely that there is no absolute threshold GFR for risk but rather a continuum with substantially lower risk at higher GFR.

Children under one year of age, have a physiologically low GFR yet no case of NSF has been reported in a patient under the age of 6 years. While it appears likely that additional factors other than a low GFR alone contribute to NSF, it is still considered by some as prudent to treat children less than 1 year of age and pregnant patients as also being at increased risk. In the past, some recommended caution in lactating patients because of the hypothetical risk of gadolinium excretion into breast milk; however it has been shown that, for at least some gadolinium-based agents, the proportion entering the breast milk is very small (nI the order of 1% of the injected dose), and very little of this is actually absorbed. Hence the risk to the child would appear negligible.

Patients with co-existing severe liver disease and renal impairment, and renal impairment of any severity in patients within one month of liver transplant (before or after), are also regarded as being at increased risk. Chronic liver disease by itself does not appear to carry any increase in risk.

2.3 Clinical features & evolution

Onset typically occurs within days (occasionally hours) of gadolinium-based contrast injection, with pain, itch, swelling, and erythema in the affected part – most often a dependent region, particularly the lower limbs. Definitive diagnosis requires lesion biopsy – clinical features are mimicked by conditions such as scleromyxoedema. The lesions evolve into fibrous plaques in the dermis and subcutaneous tissues; plaques have also been reported in muscle (incl. diaphragm), heart, liver, and lung. Plaques in the limbs can cause crippling contractures.

A small number of cases appear to have a rapidly progressive course, but the disease contributes to death in a substantial proportion of cases.

2.4 Treatment

The best responses have been seen in patients whose renal function has been substantially improved, eg. by transplant. Many other treatments are being tried, so far without a clear-cut preferred treatment emerging.

2.5 Are there any Australian cases?

There are reported cases in both Australia and New Zealand\(^1\). Cases should be reported to the Therapeutic Goods Administration (see http://www.tga.gov.au/safety/problem.htm), and to the manufacturer of any potentially implicated contrast agent.
2.6 Which agents have been implicated?

Cases reported in the peer-reviewed literature have been associated most often with exposure to gadodiamide (Omniscan), followed by gadopentetate (Magnevist) and gadoversetamide (Optimark). It is emphasised that absolute numbers of cases do not necessarily reflect the relative risks of these agents, as they do not take account of the relative frequency of use of the various agents; Magnevist and Omniscan were the market leaders world-wide, and anecdotally Omniscan has sometimes been preferred in renal units because of its “non-ionic” formulation.

Small numbers of cases, often unconfirmed, have been reported in patients who have received gadobenate (MultiHance), gadobutrol (Gadovist) gadoterate (Dotarem), or gadoteridol (ProHance), though most of these have been confounded by the fact that the same patients also received one or more doses of other agents more often associated with NSF. At the time of writing, no confirmed cases of NSF had been established after unconfounded exposure to gadobenate (MultiHance) or gadoterate (Dotarem). The possibility that each of these 4 agents could be associated with the development of NSF has certainly not been excluded, though it seems on the available evidence that any such association would be very rare. Experience with gadoxetate (Primovist) and gadofosveset (Ablavar) remains very limited.

2.7 What is the pathogenesis?

A bone-marrow-derived fibrocyte seems to be central to the pathobiology of the condition. It is not known what triggers its abnormal behaviour, however two lines of evidence have been presented that implicated loss of gadolinium from the chelating agent:

(i) Animal studies have shown that biological clearance of gadolinium after injection of less stable chelates is much slower than after injection of more stable (cyclic) chelates;

(ii) Chemical analysis of NSF plaques in clinical cases has found relatively high levels of inorganic (ie de-chelated and subsequently metabolised) gadolinium.

It is emphasised that, while suggestive, these observations do not prove a mechanism involving de-chelation and/or transmetallation to be the pathway to NSF. Experiments in cell culture have shown that gadolinium chelates can stimulate fibroblast proliferation and enzyme activation, with the agents more commonly implicated in NSF showing these effects at much lower concentration thresholds. The precise mechanism of these effects has not yet been established.

2.8 Which chelates are more “stable”?

Chelate stability is reported in several ways, reflecting different parameters affecting the equilibrium between gadolinium ions, their ligands, and chelated ions; some are more relevant to laboratory conditions, others attempt to reflect biological conditions. In general, chelates with a cyclic structure (gadoterate, gadoteridol, gadobutrol) are more stable than linear molecules such as gadobenate, gadodiamide, gadopentetate, and gadoversetamide. Gadodiamide and gadoversetamide are less stable chelates than the other linear agents. This ranking has recently been confirmed in studies in human serum at physiological temperatures and pH. It should be noted, however, that although gadobenate (MultiHance) has a similar stability profile to the other linear chelates, clinical data suggest that it is never the less associated with a very low risk of NSF.
3. RECOMMENDATIONS

3.1 Risk Factors for Kidney Disease

All patients for whom the use of a gadolinium-based MRI contrast agent is being considered should be screened for the presence of kidney disease. Screening should include review of available medical records, as well as questioning of the patient (or relatives and acquaintances where the patient is unable to respond appropriately). Relevant indicators to be sought include:

- Previous laboratory tests (GFR, serum creatinine, eGFR)
- Known history of kidney disease or dialysis
- Known family history of renal disease
- Age > 60 years
- Aboriginal or Torres Strait Islander (ATSI) ethnicity
- History of diabetes
- History of vascular disease – previous AMI or stroke
- Hypertension
- History of smoking
- BMI > 30

3.2 Formal Assessment of Kidney Function

If one or more of the above risk factors for kidney disease are present, and there is no recent (<3 months for stable outpatients; <7 days for stable inpatients) laboratory tests are available, serum creatinine should be obtained and an eGFR estimated on all patients having an MRI scan with contrast. Following estimation of eGFR, risk stratification should be performed as detailed in point 5.

3.3 eGFR Measurement Reliability

Situations where eGFR measurement is an unreliable marker of GFR include AKI (Acute Kidney Injury) (note that serum creatinine may not stabilize until 7-10 days after an acute insult), peri-operative liver transplant patients, patients with “hepato-renal syndrome”, and patients with chronic liver disease where eGFR may overestimate true GFR. These patients are at significant risk for NSF, but the size of this risk remains poorly quantified at this time.

3.4 Alternative Imaging Modality

Consider whether any other imaging modality – including non-contrast MRI, CT, or ultrasound – could provide the required diagnostic information at less risk. CT using iodinated contrast may be considered as an alternative, but also has risks including ionising radiation exposure, and, in patients with CKD, contrast nephropathy with potential permanent loss of residual renal function. Do not use MRI contrast agents for CT or conventional angiography in an attempt to avoid nephrotoxicity.

No patient should be denied any imaging investigation that is critical to clinical management.

3.5 High Risk Patients

In high risk patients, ie those in groups 3.6.4-6 below, where the perceived benefit of an MRI scan outweighs the risks it is recommended that:

(a) The minimum adequate dose of gadolinium is used.

There is evidence for a dose-risk relationship. Restrict dose to 0.1 mmol/kg and avoid repeat scans.
(b) Consider immediate post-scan haemodialysis.

A single conventional haemodialysis session will remove 75% of the free Gadolinium - a 2nd treatment 93% and a 3rd treatment 98% of a dose.

If the patient has severe renal failure, but is not receiving haemodialysis, the possibility of commencing haemodialysis will need individual consideration. To date, it is not known whether early haemodialysis post-procedure reduces the risk of NSF.

(c) Use a contrast agent with the lowest theoretical risk.

Choices which may reduce the risk include:

(i) use of the theoretically most stable chelates (those with a cyclic molecular structure)

(ii) use of agents with higher relaxivity, allowing smaller doses of gadolinium for the same T1 shortening effect.

3.6 Risk Stratification

Risk stratification is performed according to clinical assessment and reported eGFR.

3.6.1 Stage 1 and 2 CKD - GFR> 60 ml/min/1.73m2 + No recognized risk factors for kidney disease

There is currently no evidence of increased risk from any of the marketed agents. There is a potential risk in individuals without risk factors but with undiagnosed kidney disease. There is also a theoretical risk of accumulation of gadolinium from higher risk chelates that should be borne in mind.

3.6.2 Stage 3 CKD - GFR 30 – 60 ml/min/1.73 m2

At milder levels of renal impairment, the risk of NSF appears extremely small. There remains a theoretical possibility of late and/or cumulative effects from gadolinium-based agents, perhaps related to persistence of small amounts of de-chelated gadolinium in tissues. Caution with the use of less stable higher risk chelates - gadodiamide, gadoversetamide, and gadopentetate – may be appropriate in this group, particularly in patients who are pregnant or lactating.

3.6.3 Stage 4 CKD – GFR 15-30 ml/min/1.73 m2

These patients are at low risk for NSF (in the order of 0.1% per dose).

Higher risk chelates (gadodiamide, gadoversetamide, gadopentetate) are contra-indicated in this group and other agents should only be used after careful consideration.

3.6.4 Stage 5 CKD - GFR< 15 ml/min/1.73 m2

These patients are at significant risk for NSF (in the order of 1% per dose).

Higher risk chelates (gadodiamide, gadoversetamide, gadopentetate) are contra-indicated in this group and other agents should only be used after careful consideration.
3.6.5 Haemodialysis:

These patients are at high risk for NSF (greater than 1 % per dose).

The risk of CT with iodinated contrast agents may well be less than that of a gadolinium-enhanced MRI examination. If a patient is anuric, there is no longer a risk of nephrotoxicity.

If the benefit of a contrast-enhanced MRI examination is felt to outweigh the risk, and CT cannot be effectively substituted, use the minimum necessary dose of, an agent with a low frequency of NSF cases.

The MRI examination should be scheduled immediately before a dialysis session, to maximise clearance of the agent, and the possibility of a second session within 24 hours, and perhaps a third additional session, should also be considered. To date, it is not known whether early haemodialysis reduces the risk of NSF.

Avoid intravenous iron therapy at time of scan, as iron theoretically may displace Gadolinium from its chelating agent.

3.6.6 Peritoneal dialysis

These patients are at the highest risk for NSF

Avoid all gadolinium-based MRI contrast agents in patients receiving peritoneal dialysis. Patients on peritoneal dialysis have both reduced clearance of the Gadolinium and increased volume of distribution; in one study, their measured risk of NSF was seven times higher than that of haemodialysis patients)¹

In a case report in a single anuric chronic peritoneal dialysis patient, 90 percent of 0.1 mmol/kg of gadodiamide was removed from the circulation in two days with a regimen of 10 to 15 exchanges per day of peritoneal dialysis²

If haemodialysis cannot be performed, we suggest more frequent peritoneal dialysis cycles for at least 48 hours after exposure, with no periods with a dry abdomen³.

3.6.7 Written report

For any contrast-enhanced MRI examination, the name of the agent used, and the dose, must be recorded in the patient record and/or the report of the examination.

3.6.8 Consent

In patients who would normally receive gadolinium for their MRI examination, but who are at risk for NSF as defined in 3.3 and 3.6.3-6, the risks and benefits of gadolinium injection, or its being withheld, should be explained and formal written consent to the chosen course of action should be documented..

3.6.9 Patient Questionnaires

Where patient questionnaires are used to screen for renal disease, consideration should be given to periodic audit of their sensitivity, e.g. by comparison to routine eGFR testing.
4. **FURTHER INFORMATION**


5. **RELATED POLICY DOCUMENTS**

- **[RANZCR Guidelines for Iodinated Contrast Administration – 2009 Edition](#)**

6. **APPENDICES**

A. Risk Factors for CKD – Flowchart
B. Gadolinium-based MR Contrast Agent: Nomenclature
C. Chelate Properties

7. **REFERENCES**

3. UpTo Date 2012
Appendix A - Flowchart for Clinical Decision-making

Risk Factors for CKD
- Known kidney disease or dialysis
- Known family history of kidney disease
- Age 60 years or older
- Diabetes
- CVD (MI or stroke)
- Hypertension
- BMI >=30
- Smoker
- ATSI

Is MRI clinically indicated?
- Yes
- No

Can MRI be performed without the use of contrast?
- Yes
- No

Unstable renal function?
- Yes
- No

Are there any risk factors for chronic kidney disease (CKD)?
- Yes
- No

Perform MRI using lowest possible dose of contrast
- eGFR > 60 ml/min/1.73m²
- eGFR 30-60 ml/min/1.73m²
- eGFR 15-30 ml/min/1.73m²
- eGFR <15 ml/min/1.73m²

Formal measurement of serum creatinine

Use of low risk contrast agents only after consideration of risks and benefits

Perform MRI without contrast

Alternative imaging

Risk of NSF 0.1%/dose: Higher risk chelates (gadodiamide, gadoversetamide, gadopentetate)

Risk of NSF 1%/dose: Higher risk chelates contraindicated.

Risk of NSF 1%/dose: Higher risk chelates contraindicated. Immediate post-procedure haemodialysis recommended

Avoid all gadolinium-based MRI contrast agents in patients receiving peritoneal dialysis
Appendix B

Gadolinium-based MR Contrast Agent: Nomenclature

By Generic Name:

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>gadobenate</td>
<td>MultiHance</td>
<td>Bracco</td>
</tr>
<tr>
<td>gadobutrol</td>
<td>Gadovist</td>
<td>BayerScheringPharma</td>
</tr>
<tr>
<td>gadodiamide</td>
<td>Omniscan</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>gadofosveset</td>
<td>Ablavar</td>
<td>Lantheus Medical Imaging</td>
</tr>
<tr>
<td>gadopentetate</td>
<td>Magnevist</td>
<td>BayerScheringPharma</td>
</tr>
<tr>
<td>gadoterate</td>
<td>Dotarem</td>
<td>Guerbet</td>
</tr>
<tr>
<td>gadoteridol</td>
<td>ProHance</td>
<td>Bracco</td>
</tr>
<tr>
<td>gadoversetamide</td>
<td>Optimark</td>
<td>Covidien (formerly Tyco)</td>
</tr>
<tr>
<td>gadoxetate</td>
<td>Primovist</td>
<td>BayerScheringPharma</td>
</tr>
</tbody>
</table>

By Trade Name:

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablavar</td>
<td>Lanthaus</td>
<td>gadofosveset</td>
</tr>
<tr>
<td>Dotarem</td>
<td>Guerbet</td>
<td>gadoterate</td>
</tr>
<tr>
<td>Gadovist</td>
<td>BayerScheringPharma</td>
<td>gadobutrol</td>
</tr>
<tr>
<td>Magnevist</td>
<td>BayerScheringPharma</td>
<td>gadopentetate</td>
</tr>
<tr>
<td>MultiHance</td>
<td>Bracco</td>
<td>gadobenate</td>
</tr>
<tr>
<td>Omniscan</td>
<td>GE Healthcare</td>
<td>gadodiamide</td>
</tr>
<tr>
<td>Optimark</td>
<td>Covidien</td>
<td>gadoversetamide</td>
</tr>
<tr>
<td>Primovist</td>
<td>BayerScheringPharma</td>
<td>gadoxetate</td>
</tr>
<tr>
<td>ProHance</td>
<td>Bracco</td>
<td>gadoteridol</td>
</tr>
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</table>
### Appendix C

**Chelate Properties**

<table>
<thead>
<tr>
<th>Risk of NSF</th>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Ligand Structure</th>
<th>Bonding</th>
<th>Biliary excretion</th>
<th>Relaxivity r1, /s/mM, at 1.5 T</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Omniscan</td>
<td>gadodiamide</td>
<td>Linear</td>
<td>Non-ionic</td>
<td>No</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Magnevist</td>
<td>gadopentetate</td>
<td>Linear</td>
<td>Ionic</td>
<td>No</td>
<td>3.9 – 4.1</td>
</tr>
<tr>
<td></td>
<td>Optimark</td>
<td>gadooversetamide</td>
<td>Linear</td>
<td>Non-ionic</td>
<td>No</td>
<td>4.7</td>
</tr>
<tr>
<td>Limited Experience</td>
<td>Primovist</td>
<td>gadoxetate</td>
<td>Linear</td>
<td>Di-ionic</td>
<td>50%</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>Ablavar</td>
<td>gadofosveset</td>
<td>Linear</td>
<td>Ionic</td>
<td>~ 5 %</td>
<td>19</td>
</tr>
<tr>
<td>Low</td>
<td>MultiHance</td>
<td>gadobenate **</td>
<td>Linear</td>
<td>Ionic</td>
<td>~ 3 %</td>
<td>6.3 – 7.9</td>
</tr>
<tr>
<td></td>
<td>Dotarem</td>
<td>gadoterate</td>
<td>Cyclic</td>
<td>Ionic</td>
<td>No</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Gadovist</td>
<td>gadobutrol</td>
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<td>Cyclic</td>
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<td>No</td>
<td>4.1</td>
</tr>
</tbody>
</table>

**Although gadobenate has a relatively poor stability profile, clinical experience to date suggests that it has a low risk of NSF.**
