GADOLINIUM-BASED CONTRAST AGENTS IN KIDNEY DISEASE

A COMPREHENSIVE REVIEW AND CLINICAL PRACTICE GUIDELINE ISSUED BY THE CANADIAN ASSOCIATION OF RADIOLOGY AND SUPPORTED BY THE CANADIAN SOCIETY OF NEPHROLOGY

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KEY POINTS

1. In patients with acute kidney injury (AKI), chronic kidney disease (CKD) Stage 4 or 5 (estimated Glomerular Filtration Rate [eGFR] < 30 mL/min/1.73m²) or those on dialysis, macrocyclic or newer linear (gadobenate dimeglumine and gadoxetate disodium) Gadolinium based contrast agents (GBCA) can be administered when GBCA enhanced MRI is considered necessary and no alternative test is available.

2. Informed consent should be obtained in these at-risk populations, either verbally or using a written consent form, by a physician or their delegate (including MRI technologists) citing an exceedingly low (much less than 1%) chance of developing Nephrogenic Systemic Fibrosis (NSF) using macrocyclic and newer linear GBCA.

3. Patients on dialysis should continue dialysis and hemodialysis should ideally be scheduled within 2-3 hours after GBCA administration. There is insufficient evidence to support initiating dialysis, switching from peritoneal to hemodialysis or altering dialysis regimes to further reduce the risk of NSF. Routine Nephrology consultations when GBCA is being considered in at-risk populations is not recommended.

4. In the outpatient setting, for institutions using macrocyclic and newer linear GBCA, a modified version of the 6-question Choyke questionnaire is suggested to screen for renal disease at time of MRI scheduling only. The patient should be asked about a history of dialysis at time of MRI scheduling and MRI. Age is not considered a valuable metric to screen for renal disease. In the inpatient setting, patients should continue to be screened for potential AKI irrespective of their eGFR.

5. For institutions using gadopentetate dimeglumine, gadodiamide and gadoversetamide, full screening should be performed at time of MRI scheduling and repeated again at time of MRI to maximize sensitivity for detection of renal disease. Gadopentetate dimeglumine, gadodiamide and gadoversetamide remain absolutely contraindicated in at-risk populations due to an estimated 3-7% risk of developing NSF (which may be an overestimate when standard dosing is not exceeded).
CAR CLINICAL PRACTICE GUIDELINE FOR ADMINISTRATION OF GBCA IN RENAL IMPAIRMENT

1. Use of Gadolinium Based Contrast Agents in patients with mild renal impairment with eGFR between 60 and 90 mL/min/1.73 m²
   - There is no evidence to suggest patients with mild renal impairment (CKD Stage 2) are at increased risk of NSF and no special precautions should be taken in these patients.

2. Use of Gadolinium Based Contrast Agents in patients with moderate renal impairment (eGFR between 30 and 60 mL/min/1.73 m²)
   - For patients with moderately reduced kidney function GBCA can be administered safely without any substantial risk of developing NSF or need for informed consent. The risk of developing NSF in moderate CKD is exceedingly rare.
     - Qualifying statements:
       ~ Studies reporting cases of NSF in patients receiving GBCA with eGFR above 30 mL/min/1.73 m² generally occurred in patients with AKI 24, 25.
       ~ One study reported three cases of NSF in patients with eGFR above 30 mL/min/1.73 m²; however, these patients were grouped with patients that also had Stage 4 CKD, the authors’ did not specify whether the patients had AKI or provide the patients eGFR levels. Moreover, the authors’ did not indicate when the eGFR was calculated which becomes problematic for this particular study because the range of time between measurement of Cr and MRI was up to 83 days 58. The authors did not reply to a request for this additional information.

3. Use of Gadolinium Based Contrast Agents in patients with severe CKD (eGFR less than 30 mL/min/1.73 m²) or dialysis dependent patients.
   - For patients with severely reduced kidney function and those on dialysis, examinations should be considered on a case by case basis. Alternative diagnostic tests (e.g. unenhanced MRI, CT, Ultrasound, biopsy, scintigraphic examinations etc.) should be considered before GBCA are prescribed. When another diagnostic modality is not available or considered inferior to enhanced MRI, and MRI is deemed necessary for patient care, then gadolinium enhanced examinations using macrocyclic or newer linear GBCA may be performed with patient informed consent citing an exceedingly low risk (much less than 1%) of NSF based upon available literature.
• Qualifying statements:

- Gadodiamide, gadopentetate dimeglumine and gadoversetamide are absolutely contraindicated. The risk of NSF when one of these agents is used in AKI or severe renal impairment is estimated to be between 1 and 7% \(^3\), the panel could not envision a scenario where an imaging facility in Canada which is required to perform enhanced MRI in AKI or severe CKD could not obtain a macrocyclic or a newer linear-ionic agent even if on a special-needs basis and felt that institutions should be exempt from single vendor contrast contracts in these instances.

- Double or triple dosing of GBCA should not be performed. There is a documented increase in the incidence of NSF with increased amount of GBCA administration (either at the same administration session or cumulatively) \(^7\), \(^8\), \(^9\), however, there are cases of NSF reported when patients have received standard dosing \(^3\). The panel felt there is insufficient evidence to support the notion that reducing the dose of GBCA beyond standard dosing further minimizes the risk of NSF and studies evaluating the minimum required dose of GBCA to maintain diagnostic accuracy of MRI are lacking.

- When possible, repeat contrast-enhanced MRI examinations should be delayed until sufficient time has passed to allow for excretion. Clearance of GBCA is partly agent specific and the panel suggests institutions review the clearance of their agents to establish a safe interval between repeated injections.

- Informed consent can be obtained verbally by a Radiologist or a suitable delegate (including MRI Technologists) and discussions with the patient should include references to the exceedingly low number of reported cases of NSF in patients with severe CKD using macrocyclic and newer linear agents. The panel makes no specific recommendation on use of verbal or written consent which can be an institutional decision. A sample of pertinent information to be discussed with the patient may be viewed on the CAR website. www.car.ca

- Patients should be monitored for signs and symptoms of NSF when they have received a GBCA with eGFR < 30 mL/min/1.73 m\(^2\) or are on dialysis and any potential cases reported (after histopathological confirmation of diagnosis with skin punch biopsy). We suggest monitoring be performed by the patients' regular (typically a General Practitioner) physician. Monitoring can be performed based upon patient symptomatology and with routine annual physical examinations. We suggest that monitoring occur for a two-year period following the administration of GBCA; however, a case of NSF occurring up to 9 years after administration of GBCA has been reported. The reporting of cases of potential NSF should be documented and filed with a regulatory body; we suggest Health Canada's Adverse Reaction Database.

- There is insufficient evidence to support the use of macrocyclic ionic GBCA (e.g. gadoterate meglumine) compared to macrocyclic non-ionic GBCA or macrocyclic GBCA vs newer linear (gadobenate dimeglumine and gadoxetate disodium) GBCA to reduce the risk of NSF when GBCA are administered in severe renal dysfunction. Studies evaluating the risk of NSF when selecting a GBCA in order of decreasing meta-stability are needed; however, unlikely to be sufficiently powered because the incidence of disease in patients who have received all of these agents with compromised renal function is very low. Data regarding cases of NSF with gadoxetate disodium is limited to the relatively lower number of injections compared to extracellular agents.

4. Dialysis

• In patients who are already receiving dialysis (peritoneal dialysis [PD] or hemodialysis [HD]), dialysis should continue after receiving GBCA. HD should be performed the same day as GBCA administration, ideally within 2 to 3 hours of MRI. There is insufficient evidence to support initiation of dialysis, change from PD to HD or altering dialysis prescription to reduce the risk of NSF.
• Qualifying statements:

- HD efficiently removes GBCA with about 70% clearance in one session and > 95% clearance after 3 sessions. Therefore, in patients who have received a GBCA and underwent HD, the half-life of GBCAs in circulation approaches that in an individual with normal kidney function 

- Little evidence exists on rates of NSF with differing duration between GBCA and subsequent dialysis. To minimize time of circulating GBCA and subsequent transmetallation and deposition, earlier HD might be potentially beneficial. Hence, for patients already on HD, HD should be scheduled soon after exposure, ideally within 2-3 hours after GBCA enhanced MRI.

- Multiple frequent dialysis sessions have been previously advocated to promote Gadolinium clearance, however, there are no formal studies showing that these practices reduce the incidence of NSF. The panel felt that there is insufficient evidence to support altering HD prescription to further reduce the risk of NSF after administration of either a macrocyclic or a newer linear GBCA.

- PD is less efficient than HD at gadolinium clearance. The literature regarding the use of PD to reduce the risk of NSF when a GBCA is administered is scarce and restricted primarily to case reports. Increasing the number of exchanges can increase GBCA clearance, but little empiric data exist on its effect on reducing the risk of NSF. Patients on PD also have residual kidney function, which can provide additional GBCA clearance. Thus, though increasing the number of exchanges (e.g. a temporary switch to automated or cycler PD) could hasten GBCA clearance, decisions regarding altering PD should be considered on a per-patient and institutional basis considering logistical aspects and residual kidney function.

- While HD does clear gadolinium more efficiently than PD, cases of NSF have occurred despite patients receiving HD promptly following GBCA. Temporary HD requires a central line placement with attendant cost, inconvenience, and potential complications. Thus, though it has been suggested that temporary HD could be considered after GBCA administration in patients on PD, the panel felt there is insufficient evidence to support switching patients on PD to HD to reduce the risk of NSF.

- Routine Nephrology consultation is not warranted for patients on dialysis or with eGFR < 30 mL/min/1.73 m² who are deemed to require GBCA; however, in patients who are dialysis dependent the dialysis service should be contacted to co-ordinate anticipated changes in HD scheduling and for patients on PD to consider potential alterations in PD prescription.

5. Acute Kidney Injury

• Patients with AKI should be managed similar to those with eGFR < 30 mL/min/1.73 m² (see Guideline statement 2) with the caveat that if GBCA administration can be delayed it should be until renal function stabilizes or ameliorates depending on the patients underlying cause for acute renal dysfunction.

• Qualifying statements:

- NSF has been reported in patients with AKI with a baseline eGFR > 30 mL/min/1.73 m². Since kidney function is not stable in patients with AKI, risk assessment for NSF should not be made on the basis of eGFR alone.

- Little data exist on GBCA and NSF in critically ill patients with AKI receiving continuous renal replacement therapy (CRRT) or sustained low-efficiency dialysis (SLED); however, both modalities would be anticipated to provide sufficient clearance of GBCA approximating HD over 24 hours.
6. Pediatric patients

- Pediatric patients with severely reduced kidney function (eGFR < 30 mL/min/1.73 m²), AKI or on dialysis should be managed according to Guideline 1.
  - The number of reported cases of NSF in the pediatric population is lower than in the adult population. There is no convincing evidence that pediatric patients have an increased risk compared to adults.
  - eGFR should be calculated using the bedside Schwartz equation.
  - eGFR during the neonatal period is lower especially in preterm infants and serum creatinine is not a reliable marker.

7. Screening for compromised renal function to identify at risk patients for NSF

- Outpatients: At institutions using macrocyclic agents or newer linear ionic agents, a modified version of the Choyke screening questionnaire (Table 2) is suggested to screen for renal disease at time of MRI scheduling only. At institutions using gadodiamide, gadopentetate dimeglumine and gadoversetamide, screening with the modified Choyke questionnaire is considered mandatory at time of MRI scheduling and the questionnaire should also be repeated at time of MRI to maximize detection of renal dysfunction.

- Inpatients: Inpatients should be assessed for AKI regardless of their eGFR, since eGFR is not always representative of renal function in this setting. Several helpful clinical tools include the Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) criteria.

- Qualifying statements:
  - The questionnaire developed by Choyke et al. has been shown to effectively stratify patients by risk of NSF and that answering "no" to all questions is extremely sensitive to detect patients with eGFR less than 30 mL/min/1.73m².

- For macrocyclic and newer linear GBCAs when the screening questionnaire (and subsequent serum Creatinine levels where appropriate) are obtained remote from the date of MRI, the screening process may need to be repeated to exclude the possibility of interval development of renal disease in patients screened too far in advance of GBCA administration. A specific time period between screening and MRI was not proposed by the panel; however, when a greater than three-to-six month time interval between screening and MRI has elapsed between time of screening and MRI, then repeat screening is probably warranted. Institutions using gadodiamide, gadopentetate dimeglumine and gadoversetamide should apply stricter time frames.

- The ACR manual on contrast media version 10.3 suggests optional screening for renal dysfunction with questionnaire or laboratory testing when a macrocyclic agent or gadobenate dimeglumine is being used. The panel agreed that routine screening of patients for renal dysfunction when macrocyclic or newer linear GBCAs are used may potentially be unnecessary; however, currently suggests a less rigorous screening methodology (rather than no screening at all) than what was formerly recommended by the CAR by using a modified version of the Choyke questionnaire (Table 2). Our current recommendation is in agreement with the European Society of Urogenital Radiology (ESUR) guidelines and we intend to revisit this controversial topic in two years with plans to harmonize CAR and ACR guidelines for screening pending a review of the published literature in the interim.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Structure</th>
<th>Stability (log $K_{eq}$)</th>
<th>Estimated number of global administrations (Millions)</th>
<th>Number of Unconfounded cases of NSF</th>
<th>Number of Confounded Cases of NSF</th>
<th>EMA Classification$^a$</th>
<th>FDA and ACR Classification$^b$</th>
<th>Health Canada Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide (Omniscan, GE Healthcare)</td>
<td>Linear non-ionic</td>
<td>16.9</td>
<td>47</td>
<td>438</td>
<td>90</td>
<td>High Risk</td>
<td>I</td>
<td>Absolutely Contraindicated</td>
</tr>
<tr>
<td>Gadopentetate dimeglumine (Magnevist, Bayer Pharmaceuticals)</td>
<td>Linear ionic</td>
<td>22.5</td>
<td>95</td>
<td>135</td>
<td>276</td>
<td>High Risk</td>
<td>I</td>
<td>Absolutely Contraindicated</td>
</tr>
<tr>
<td>Gadoversetamide (Optimark, Guerbet Group)</td>
<td>Linear non-ionic</td>
<td>16.6</td>
<td>0.8</td>
<td>7</td>
<td>11</td>
<td>High Risk</td>
<td>I</td>
<td>Absolutely Contraindicated</td>
</tr>
<tr>
<td>Gadobenate dimeglumine (Multihance, Bracco Pharmaceuticals)</td>
<td>Linear ionic</td>
<td>22.6</td>
<td>30</td>
<td>0</td>
<td>32</td>
<td>Medium Risk</td>
<td>II</td>
<td>May be used with extreme caution</td>
</tr>
<tr>
<td>Gadoxetate disodium (Primovist, Bayer Pharmaceuticals)</td>
<td>Linear non-ionic</td>
<td>23.5</td>
<td>4.3</td>
<td>0</td>
<td>0</td>
<td>Medium Risk</td>
<td>III</td>
<td>May be used with extreme caution</td>
</tr>
<tr>
<td>Gadoteridol (Prohance, Bracco Pharmaceuticals)</td>
<td>Macroyclic non-ionic</td>
<td>23.8</td>
<td>22</td>
<td>1 or 2</td>
<td>37</td>
<td>Low Risk</td>
<td>II</td>
<td>May be used with extreme caution</td>
</tr>
<tr>
<td>Gadoterate meglumine (Dotarem, Guerbet Group)</td>
<td>Macroyclic Ionic</td>
<td>25.8</td>
<td>65</td>
<td>0 or 1</td>
<td>7</td>
<td>Low Risk</td>
<td>II</td>
<td>N/A$^c$</td>
</tr>
<tr>
<td>Gadobutrol (Gadovist, Bayer Pharmaceuticals)</td>
<td>Macroyclic non-ionic</td>
<td>21.8</td>
<td>5.7</td>
<td>3f</td>
<td>8</td>
<td>Low Risk</td>
<td>II</td>
<td>May be used with extreme caution</td>
</tr>
</tbody>
</table>

$^a$ European Medicines Agency
$^b$ American Food and Drug Administration and American College of Radiology
$^c$ Gadoteric acid was not available for clinical use in Canada at time of most recent Health Canada update on NSF [9]
### TABLE 2

**SCREENING QUESTIONNAIRE**

Screening questionnaire to be administered to the outpatient population to identify renal disease at time of MRI scheduling (for institutions using macrocyclic agents and newer linear GBCA) and also immediately before MRI for institutions which use gadodiamide, gadopentetate dimeglumine and gadoversetamide.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever been told you have renal problems?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Have you ever been told you have protein in your urine?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Do you have high blood pressure?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Do you have diabetes?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Do you have gout?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Have you ever had kidney surgery?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Are you on dialysis?</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Pre-gadolinium screening questionnaire for identifying patients at risk of poor renal function, adapted from Choyke et al. [90].

- *Not included in the original Choyke survey but important to clarify prior to administration of GBCA. The panel suggests the question be asked to the patient at time of MRI scheduling and at time of MRI.*
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