



CAR National Advisory on Gadolinium Administration and Nephrogenic Systemic Fibrosis

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This advisory was developed through review of evidence-based research and consultations undertaken by the NSF Advisory Working Group for the CAR:

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Introduction:

In 1997, a new clinicopathological entity recognized by skin thickening and induration was described in patients with end-stage renal disease. The initial designation of Nephrogenic Fibrosing Dermopathy (NFD) was later revised once autopsy studies described widespread involvement of additional extra-cutaneous organs. Upon demonstration of collagen deposition and consequent fibrosis involving not only the skin but also skeletal muscle, lungs, heart, pulmonary vessels, diaphragm and esophagus^{1,2}, this new disease became known as Nephrogenic Systemic Fibrosis (NSF).

In 2006, exposure to gadolinium based contrast agents (GBCAs) was implicated in the pathogenesis of NSF.

NSF is a rare and potentially fatal complication of certain GBCAs affecting patients with compromised renal function³. Both the exact pathophysiology of, and importantly, a cure for NSF remain elusive. Partial clinical responses have been described following renal transplantation and hemodialysis, although no strong evidence exists in their support.

The widespread negative impact of NSF on utilization of contrast-enhanced MR imaging has clearly resonated worldwide. In response, the Canadian Association of Radiologists (CAR) Board Working Group (BWG) on NSF has developed the following guidelines to address practical issues applicable to Canadian radiologists and their patients. The CAR BWG represents a collaborative effort between radiology and nephrology. As data accumulates in various world-wide registries, these recommendations may change to reflect the most recent available evidence. Accordingly, all physicians are advised to remain current on NSF literature and future, revised guidelines.

Overview:

It is crucial that these practice guidelines be tailored to the individual patient via consultation with the referring physician, radiologist and when necessary, a nephrologist. The BWG recommends that all patients with chronic kidney disease consult their physicians regarding the risk of developing NSF following administration of GBCAs. Finally, it is imperative that clinicians recognize that NSF remains a rare complication of GBCA administration, even in high-risk patients. Therefore, considering the value of contrast-enhanced MR imaging as a diagnostic tool, it is incumbent that all physicians carefully assess the risks and benefits of GBCA administration to this patient population.

NSF is a reportable disease. All suspected cases should be reported to Health Canada Canadian Adverse Drug Reaction Monitoring Program (CADRMP) via telephone (1.866.234.2345) or by fax (1.866.678.6789).

1. What GBCAs have been implicated in NSF?

The GBCAs available for clinical use in Canada have different reported incidences of NSF. In *unconfounded* cases, NSF has developed after administration of a single GBCA. In *confounded* cases, two GBCAs have been administered within approximately eight weeks before the development of NSF.

Gadodiamide, or Gd-DTPA-BMA (Omniscan; GE Healthcare, Milwaukee, Wisconsin) accounts for 80-90% of unconfounded published and reported cases^{4,5}. NSF has also been reported with Gadopentetate Dimeglumine, or Gd-DTPA (Magnevist; Bayer Schering Pharma AG, Berlin, Germany) and Gadoversetamide, or Gd-DTPA-BMEA (OptiMARK; Mallinckrodt Inc., Hazelwood, Missouri).

No *unconfounded* cases involving more tightly-chelated GBCA's, Gadobenate Dimeglumine, or Gd-BOPTA (MultiHance; Bracco Diagnostics Inc., Princeton, New Jersey), Gadoteridol, or Gd-HP-DO3A (ProHance; Bracco Diagnostics Inc., Princeton, New Jersey), Gadofosveset Trisodium, or Diphenylcyclohexyl phosphodiester-Gd-DTPA (Vasovist; EPIX Pharmaceuticals, Lexington, Massachusetts) and Gadobutrol, or Gd-DO3A-butrol (Gadovist; Bayer Inc., Toronto, Ontario) have been reported.

2. How should renal function be assessed prior to administration of GBCAs?

It is the opinion of the BWG that is not necessary to obtain an estimated glomerular filtration rate (eGFR) in all patients scheduled for GBCA administration.

It is critical that radiologists and referring physicians be aware of the existence of *silent renal failure*. Findings from the National Health and Nutrition Examination Survey (NHANES) demonstrated that only 22% of patients with Stage 3 chronic kidney disease (CKD) and 45% of patients with Stage 4 CKD were actually aware of their renal compromise⁶. However, it should still be remembered that the non age adjusted prevalence of Stage 4 and 5 CKD in the United States is 0.4%⁷.

A pre-examination questionnaire should be accurately completed for any patient scheduled to undergo an MRI examination that could potentially require administration of contrast. A sample screening questionnaire is depicted below:

Are you over the age of 60?	Yes	No
Do you have a history of:		
Renal disease (solitary kidney, renal transplant, renal tumour)	Yes	No
Hypertension	Yes	No
Diabetes	Yes	No
Stroke	Yes	No
Myocardial infarction	Yes	No
Peripheral Vascular disease	Yes	No
Organ transplantation	Yes	No
Chemotherapy for malignancy	Yes	No

If the screening form reveals risk factors for CKD, the eGFR should be calculated from serum creatinine using the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formulae.

Patients whose renal function is known are exempt from such screening. An eGFR obtained within 3 months for outpatients, as long as no interval hospitalization has occurred, or within 48 hours for inpatients is acceptable.

GBCA administration can be hazardous for patients with acute kidney injury (AKI), the severity of which may not be accurately reflected in the most recent available eGFR. If AKI is suspected, nephrology consultation is recommended to accurately assess the patient's renal function.

Some MR centres use GBCA at higher doses than recommended by the manufacturer ('off-label' use). While the CAR cannot condone this practice, it is acknowledged that such doses are administered in certain exams (e.g. cardiac MRI, MR angiography, MR urography, and breast MRI). It is strongly recommended that renal function be determined prior to performing these studies in all patients, regardless of risk factors.

3. Is GBCA dose adjustment necessary in patients with CKD?

As a rule, the lowest possible dose to achieve a diagnostic examination should always be used.

For patients with Class 3 CKD (eGFR 30-60 mL/min/1.73m²):

Excluding patients with AKI, the risk of developing NSF with exposure to GBCAs is exceptionally low in the stable patient, assuming an accurate assessment of renal function has been made⁸. Therefore, adjustment of dose and specific discussion of the risk of NSF is not required in this group.

For patients with Class 4 or 5 CKD (eGFR <30 mL/min/1.73m²):

In this higher risk group, it is important to confirm that the GBCA enhanced examination is indeed necessary and that other imaging tests (i.e. non contrast MRI, non-contrast CT or ultrasound) would not provide the required information. *However, physicians should not deprive at-risk patients of clinically indicated contrast enhanced MR examinations.* Therefore, if such an examination is deemed critical to guide future clinical management, it is recommended that a nephrology consultation be considered for patients with an eGFR <30 mL/min/1.73m² as long as the MR examination can be delayed to allow such a consult without adversely affecting the patient outcome. This recommendation for nephrology involvement may be subject to regional nephrology opinion.

Gadodiamide (Omniscan), Gadopentetate Dimeglumine (Magnevist) and Gadoversetamide (OptiMARK) are to be avoided in patients with an eGFR <30 mL/min/1.73m². Instead, the use of a tightly chelated agent is recommended at the lowest dose that yields a diagnostic study.

In patients with Class 4 or 5 CKD, informed consent should be obtained prior to administration of GBCAs. The consent should include an estimate of the risk of NSF following GBCA administration, a description of the signs and symptoms of NSF and possible sequelae, as well as the timeline of signs and symptoms following GBCA administration. The effectiveness of current treatments for NSF, namely hemodialysis and renal transplantation, should also be discussed. The importance of diagnostic information provided by contrast enhanced MR in directing further management should be emphasized. Patients should be instructed to seek urgent medical attention should the symptoms develop.

To enhance the knowledge of referring physicians and hospital house-staff regarding NSF, it is recommended that any patient scheduled for a contrast enhanced MRI with an eGFR <30 mL/min/1.73m² should first be provided with the above information at least several days prior to his or her appointment (either by fax or reference to website content) to optimize the informed consent process.

Repeated administration of GBCAs has been shown to be a risk factor in the development of NSF. Repeated use of GBCAs in patients with abnormal eGFR values, especially within a short interval up to one week, should be undertaken with caution.

In patients with chronic kidney disease, physicians should strongly consider the risks of using GBCAs instead of iodinated contrast in examinations such as CT or diagnostic angiography in an effort to prevent contrast-induced nephropathy (CIN). The risk of NSF, although probably lower than CIN, remains an important consideration in these patients.

4. What is the role of renal protective measures in NSF?

Currently, there is no data to corroborate the institution of renal protective protocols such as aggressive hydration or bicarbonate administration in patients at risk of NSF.

Hemodialysis has been shown to effectively remove GBCA from the circulatory system with approximately 98% eliminated after three dialysis sessions⁹. While the BWG recognizes that hemodialysis may not prevent NSF, hemodialysis should be considered in patients with an eGFR <30 mL/min/1.73m² following GBCA administration.

All contrast-enhanced MR examinations in patients on dialysis (hemo- or peritoneal) should be organized in collaboration with the nephrologist. Given that these dialysis dependent patients represent the cohort most at risk for NSF, hemodialysis is recommended as soon as possible following GBCA administration.

5. Are there any guidelines regarding paediatric and obstetrics patients?

This Advisory is primarily directed towards the non-obstetrical and non-paediatric age groups. eGFR is not routinely required in either of these groups, and it should be remembered that the accuracy of such measures in these patients can be compromised^{10,11}. Nevertheless, the usual consideration of risks and benefits of MRI and Gd-enhanced MRI should occur.

For example, a subgroup of paediatric patients are expected to have many Gd-enhanced MR imaging studies over their childhood and adolescence. Many receive treatments such as chemotherapy and bone marrow transplantation which can impair their renal function. As estimation of GFR using serum creatinine levels in children and neonates is not optimal, and since little data is available regarding the incidence of NSF in this age group, this clinical scenario will be subject to regional opinion regarding the need for Paediatric Nephrology consultation prior to repeated administration of GBCAs, and will require specific discussion in future Advisories.

Conclusion:

It is important to re-iterate that these practice guidelines be tailored to the individual patient's specific clinical circumstance. Given the powerful diagnostic potential of contrast-enhanced MRI, if the benefits of GBCA administration are outweighed by the risks, the aforementioned guidelines provide a framework for the appropriate work-up and management of patients with CKD.

References:

1. Cowper SE, Robin HS, Steinberg HM, et al. Scleromyxoedema-like cutaneous disease in renal-dialysis patients. *Lancet* 2000;356:1000-1001.
2. Gibson SE, Farver CF, Prayson RA. Multiorgan involvement in Nephrogenic Fibrosing Dermopathy; an autopsy case and review of the literature. *Arch Path Lab Med* 2006; 130:209-212.
3. Cowper SE. Nephrogenic Systemic Fibrosis: An Overview. *J Am Coll Radiol* 2008; 5:23-28.
4. Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR Contrast Agents and Nephrogenic Systemic Fibrosis. *Radiology* 2007; 242(3):647-649.
5. Broome DR. Nephrogenic Systemic Fibrosis associated with gadolinium based contrast agents: A summary of the medical literature reporting. *Eur J Radiol* 2008 May;66(2):230-234.
6. Nickolas TL, Frisch GD, Opotowsky AR, et al. Awareness of kidney disease in the US population: Findings from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000. *Am J Kidney Dis* 2004; 44:185-197.
7. CDC. Prevalence of Chronic Kidney Disease and Associated Risk Factors – United States 1999-2004. *MMWR* 2007 Mar;56(08):161-165.
8. Weinreb JC. Impact on Hospital Policy: Yale Experience. *J Am Coll Radiol* 2008;5:53-56.
9. Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acta Radiol* 1998;5:491-502.
10. Alper AB, Yi Y, Webber LS, et al. Estimation of glomerular filtration rate in preeclamptic patients. *Am J Perinatol* 2007 Nov; 24(10):569-574.
11. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatr Nephrol* 2007; 22:1839-1848.